KDIGO 2022 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANGEMENT IN CHRONIC KIDNEY DISEASE

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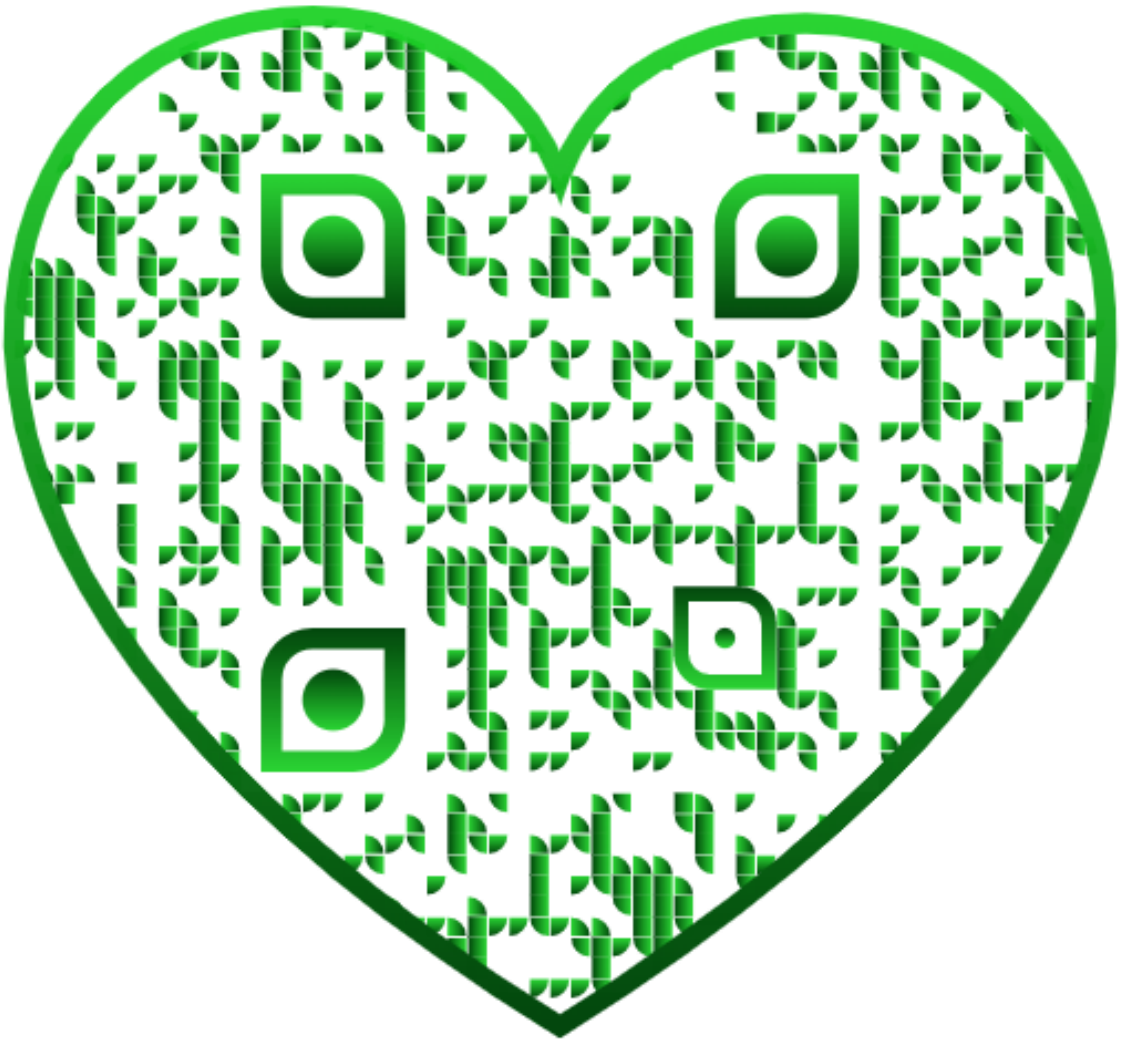
PUBLIC REVIEW DRAFT

MARCH 2022



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REFERENCE KEYS

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of recommendation is indicated as **Level 1** or **Level 2**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1, "Strong" "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2, "Weak" "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Grade	**Quality of evidence**	**Meaning**
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is <u>defined</u> as abnormalities of kidney structure or function, present for > 3 months, with implications for health. CKD is <u>classified</u> based on <u>C</u>ause, <u>G</u>FR category (G1-G5), and <u>A</u>lbuminuria category (A1-A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	< 15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI Unit
Creatinine	mg/dl	88.4	µmol/l
Glucose	mg/dl	0.0555	mmol/l

Note: Conventional unit x conversion factor = SI unit

ALBUMINURIA CATEGORIES IN CKD

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	ACR (approximate equivalent) (mg/g)	Terms
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased[a]
A3	>300	>30	>300	Severely increased[b]

ACR, albumin-to-creatinine ration; AER, albumin excretion rate; CKD, chronic kidney disease
[a]Relative to young-adult level
[b]Including nephrotic syndrome (AER usually >2200 mg/24 h [ACR >2200 mg/g; > 220 mg/mmol])

HbA1c CONVERSION CHART

DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
5.0	31	6.0	42	**7.0**	**53**	**8.0**	**64**	9.0	75
5.1	32	6.1	43	7.1	54	8.1	65	9.1	76
5.2	33	6.2	44	7.2	55	8.2	66	9.2	77
5.3	34	6.3	45	7.3	56	8.3	67	9.3	78
5.4	36	6.4	46	7.4	57	8.4	68	9.4	79
5.5	37	**6.5**	**48**	**7.5**	**58**	8.5	69	9.5	80
5.6	38	6.6	49	7.6	60	8.6	70	9.6	81
5.7	39	6.7	50	7.7	61	8.7	72	9.7	83
5.8	40	6.8	51	7.8	62	8.8	73	9.8	84
5.9	41	6.9	52	7.9	63	8.9	74	9.9	85
DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)	DCCT (%)	IFCC (mmol/mol)
10.0	86	11.0	97	12.0	108	13.0	119	14.0	130
10.1	87	11.1	98	12.1	109	13.1	120	14.1	131
10.2	88	11.2	99	12.2	110	13.2	121	14.2	132
10.3	89	11.3	100	12.3	111	13.3	122	14.3	133
10.4	90	11.4	101	12.4	112	13.4	123	14.4	134
10.5	91	11.5	102	12.5	113	13.5	124	14.5	135
10.6	92	11.6	103	12.6	114	13.6	125	14.6	136
10.7	93	11.7	104	12.7	115	13.7	126	14.7	137
10.8	95	11.8	105	12.8	116	13.8	127	14.8	138
10.9	96	11.9	107	12.9	117	13.9	128	14.9	139

IFCC–HbA1c (mmol/mol) = [DCCT–HbA1c (%) – 2.15] × 10.929.
DCCT, Diabetes Control and Complications Trial; HbA1c, glycated hemoglobin; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine.
Source: Diabetes UK, www.diabetes.org.uk.

ABBREVIATIONS AND ACRONYMS

ACEi	angiotensin-converting enzyme inhibitor(s)
ACR	albumin-creatinine ratio
AKI	acute kidney injury
ARB	angiotensin II-receptor blocker
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CGM	continuous glucose monitoring
CI	confidence interval
CKD	chronic kidney disease
CrCl	creatinine clearance
CVD	cardiovascular disease
DPP-4	dipeptidyl peptidase 4
eGFR	estimated glomerular filtration rate
ERT	Evidence Review Team
ESKD	(In accordance with KDIGO nomenclature, all instances of end-stage kidney disease [ESKD] have been replaced with "kidney failure")
FDA	Food and Drug Administration
GFR	glomerular filtration rate
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide-1 receptor agonist(s)
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HbA1c	glycated hemoglobin
HFpEF	heart failure and preserved ejection fraction
HFrEF	heart failure and reduced ejection fraction
HR	hazard ratio
K+	serum potassium
KDIGO	Kidney Disease: Improving Global Outcomes
MACE	major adverse cardiovascular events
MRA	mineralocorticoid receptor antagonist
NHANES	National Health and Nutrition Examination Survey
OR	odds ratio
PICOM	population, intervention, comparator, outcomes, and methods
RAS(i)	renin-angiotensin system (inhibitor)
RCT	randomized controlled trial
RR	relative risk
SCr	serum creatinine
SGLT2i	sodium-glucose cotransporter 2 inhibitor(s)
SMBG	self-monitoring of blood glucose
T1D	type 1 diabetes
T2D	type 2 diabetes
UKPDS	United Kingdom Prospective Diabetes Study Group
US	United States

NOTICE

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based upon literature searches last conducted in December 2021. It is designed to assist decision making. It is not intended to define a standard of care, and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Health-care professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section, and is kept on file at KDIGO.

Note: This draft version of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease is *not final*. Please do not quote or reproduce any part of this document.

FOREWORD

With the growing awareness that chronic kidney disease (CKD) is an international health problem, Kidney Disease: Improving Global Outcomes (KDIGO) was established in 2003 with its stated mission to "improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines."

The prevalence of diabetes around the world has reached epidemic proportions. The International Diabetes Federation estimated that 537 million people were living with diabetes in 2021. This number is expected to increase to 784 million by 2045. It has been estimated that 40% or more of people with diabetes will develop CKD, including a significant number who will develop kidney failure requiring dialysis and transplantation.

With a number of new agents targeting a variety of mechanistic approaches to improving outcomes for people with diabetes and kidney disease, KDIGO published its first guideline for Diabetes Management in CKD in 2020. However, in just under 2 years, the development of additional treatments and the continued publication of high-quality trials in patients with diabetes and CKD warranted a review of the original 2020 guidance to help clinicians and patients implement these new advances.

We once again thank Ian de Boer, MD, MS and Peter Rossing, MD, DMSc for leading this important initiative and we are especially grateful to the continued dedication of the original Work Group members who provided their time and expertise to this update. In addition, we thank the independent Evidence Review Team (ERT) from Cochrane Kidney and transplant led by Jonathan Craig, MBChB, DipCH, FRACP, M Med (Clin Epi), PhD and David Tunnicliffe, PhD who were tasked with updating the evidence review informing the latest version of the guideline.

In keeping with KDIGO's policy for transparency and rigorous public review during the guideline development process, the draft guideline here is now made available for open commenting. The feedback received from the public review will be carefully considered by the Work Group members and the guideline will be revised as appropriate for the final publication.

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ABSTRACT

The Kidney Disease: Improving Global Outcomes (KDIGO) 2022 Clinical Practice Guideline on the Diabetes Management in Chronic Kidney Disease represents a focused update of the KDIGO 2020 guideline on the topic. The guideline targets to a broad audience of clinicians treating diabetes and CKD while being mindful of implications for policy and payment. Topic areas for which recommendations are updated include: Chapter 1: Comprehensive care in patients with diabetes and CKD and Chapter 4: Glucose-lowering therapies in patients with type 2 diabetes (T2D) and CKD. Previous chapters on glycemic monitoring and targets in patients with diabetes and CKD (Chapter 2), lifestyle interventions in patients with diabetes and CKD (Chapter 3), and approaches to management of patients with diabetes and CKD (Chapter 5) have been deemed current and their content has remained unchanged. Development of this guideline update followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the quality of the evidence and the strength of recommendations followed the 'Grading of Recommendations Assessment, Development and Evaluation' (GRADE) approach. Limitations of the evidence are discussed, with areas of future research also presented.

Keywords: angiotensin-converting enzyme inhibitor; angiotensin II receptor blocker; chronic kidney disease; dialysis; evidence-based; GLP-1 receptor agonist; glycemia; glycemic monitoring; glycemic targets; guideline; HbA1c; hemodialysis; KDIGO; lifestyle; metformin; models of care; nutrition; renin-angiotensin system; self-management; SGLT2 inhibitor; systematic review; team-based care

INTRODUCTION FROM THE GUIDELINE CO-CHAIRS

The KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease (CKD) follows only 2 years after the original 2020 Clinical Practice Guideline on this topic. The update was motivated by the wealth of high-quality new information that has quickly become available since the original 2020 guideline was published and by calls from the community to help guide application of these new data. The short interval between guidelines reflects the rapid pace of advancement in treatment of diabetes and CKD.

A comprehensive process was undertaken to update the guideline. The Evidence Review Team (ERT) first updated the systematic literature search for each topic covered by the 2020 guideline. The Work Group reviewed the ERT summary of new studies by topic and judged by topic whether there was sufficient new evidence to conduct a full quantitative reassessment with reconsideration of recommendations. Such full reassessments were deemed warranted for use of sodium-glucose co-transporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and mineralocorticoid receptor antagonists (MRAs). For these topics, the ERT updated the detailed extraction and meta-analysis of available data, and the Work Group revised the corresponding guideline chapters accordingly.

Updates to sections on SGLT2i and GLP-1 RA include new data, additional discussion, modification of the SGLT2i recommendation to reflect new evidence of benefits and safety with eGFR ≥20 ml/min per 1.73 m^2 (from ≥30 ml/min per 1.73 m^2 previously) among people with type 2 diabetes, and revised or added practice points and research recommendations. In addition, the SGLT2i section was moved from the glycemic control section to the comprehensive care section to reflect growing acknowledgement that these drugs are an essential component of CKD care irrespective of glycemic effects. These changes were supported by multiple new large randomized controlled trials assessing the benefits and risks of SGLT2i and GLP-1 RA.

A new section on MRA was added to the chapter on “Comprehensive care in patients with diabetes and CKD”, with a new recommendation supporting use of nonsteroidal MRAs for patients with type 2 diabetes, residual albuminuria despite first-line treatments for diabetes and CKD, and normal serum potassium concentration. This section and recommendation were indicated largely by two new trials evaluating the benefits and risks of finerenone, a novel nonsteroidal MRA.

As for the 2020 guideline, the 2022 guideline is designed to apply to a broad population of patients with diabetes and CKD. T1D and T2D are both addressed, with differences in approach to management highlighted when appropriate. Pharmacologic management of glycemia is one aspect of care that differs substantially by diabetes type. The guideline includes evidence-based recommendations for pharmacologic antihyperglycemic treatment in T2D and CKD but defers pharmacologic glucose-lowering treatment of T1D, based on insulin, to existing guidelines from diabetes organizations. Similarly, the Work Group addressed care for patients with all severities of CKD, patients with a kidney transplant, and patients treated with hemodialysis or peritoneal dialysis. CKD is defined as persistently elevated urine albumin excretion (≥30 mg/g [3 mg/mmol] creatinine), persistently reduced estimated glomerular filtration rate (eGFR <60 ml/min per 1.73 m^2), or both, for greater than 3 months, in accordance with current KDIGO guidelines.

This is an evidence-based guideline that focuses on clinical management questions that can be addressed with high-quality scientific evidence. Specifically, we focused on questions that have been addressed using randomized trials that evaluated clinically relevant outcomes. This guideline is not a textbook. Our approach omits important aspects of clinical care that have become standard practice but are not addressed with randomized trials—for which we refer readers to excellent existing texts and reviews—as well as new treatments that are yet insufficiently evaluated for application to clinical care.

Concurrent with the 2022 guideline, KDIGO partnered with the American Diabetes Association (ADA) to issue a consensus report on the diagnosis and management of diabetes and CKD. This report demonstrates the broad similarities across evidence-based recommendations from the 2 professional societies and emphasizes high-priority interventions to improve the health of people with diabetes and CKD. In addition, the consensus report addresses aspects of CKD prevention, screening, and diagnosis that are important clinical topics not explicitly covered in the KDIGO guideline.

Diagnostically, CKD occurring among people with diabetes is usually attributed to diabetes, unless other causes are readily evident. Certainly, cases of CKD occurring among people with diabetes are actually heterogeneous, and some are caused by other processes. More work is needed to develop granular approaches to CKD diagnosis and classification in diabetes and to determine the roles of kidney biopsy and biomarkers in this evaluation. Here, we adopt the current clinical approach of treating most presentations of diabetes and CKD similarly, modifying the approach as appropriate according to albuminuria or eGFR category. We avoid the term “diabetic kidney disease” to avoid the connotation that CKD is caused by traditional diabetes pathophysiology in all cases, although this term is entirely appropriate when this limitation is recognized. We also avoid the term “diabetic nephropathy,” an outdated term for which there is currently no consensus definition. Prevention, screening, and diagnosis of new-onset diabetes after transplantation are also important topics that were considered out of scope for this guideline.

The care of patients with diabetes and CKD is multifaceted and complex, as highlighted in our first chapter, “Comprehensive care in patients with diabetes and CKD.” Several critical aspects of this comprehensive care, such as blood pressure and lipid management, were addressed in other KDIGO guidelines. These topics were not reviewed for the current guideline, and we refer readers to prior KDIGO guidelines and the ADA-KDIGO consensus report. Fortunately, new treatments relevant to people with diabetes and CKD are currently being developed. However, such treatments were not included in this guideline if well-powered randomized trials with clinical outcomes have not yet been reported.

The Work Group aimed to generate an updated guideline that is both rigorously devoted to existing evidence and clinically useful. The group made recommendations only when they were supported by high-quality evidence from a systematic review generated by the ERT. However, practice points were made when evidence was insufficient to make a recommendation but clinical guidance was thought to be warranted. In some situations, recommendations could be made for some groups of patients but not others. For example, evidence for patients treated with dialysis was often weak, leading to fewer recommendations for this population.

Fortunately, almost all members of the Work Group, ERT, and KDIGO staff who contributed to the 2020 guideline agreed to also contribute to the 2022 guideline. As Co-Chairs, we would like to recognize the outstanding efforts of all of these dedicated contributors, without whom this guideline would not have been possible. The Work Group was diverse, multinational, multidisciplinary, experienced, thoughtful, and vigilant in its work. Notably, the Work Group included 2 members who have diabetes and CKD who contributed actively as peers to keep the guideline relevant and patient-centered. Incorporating patients as partners has become more common in research, and we are pleased to see that this model is being adopted by additional clinical practice guidelines. We hope that the summary guidance provided here will help improve the care of patients with diabetes and CKD worldwide.

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Diabetes Guideline Co-Chairs

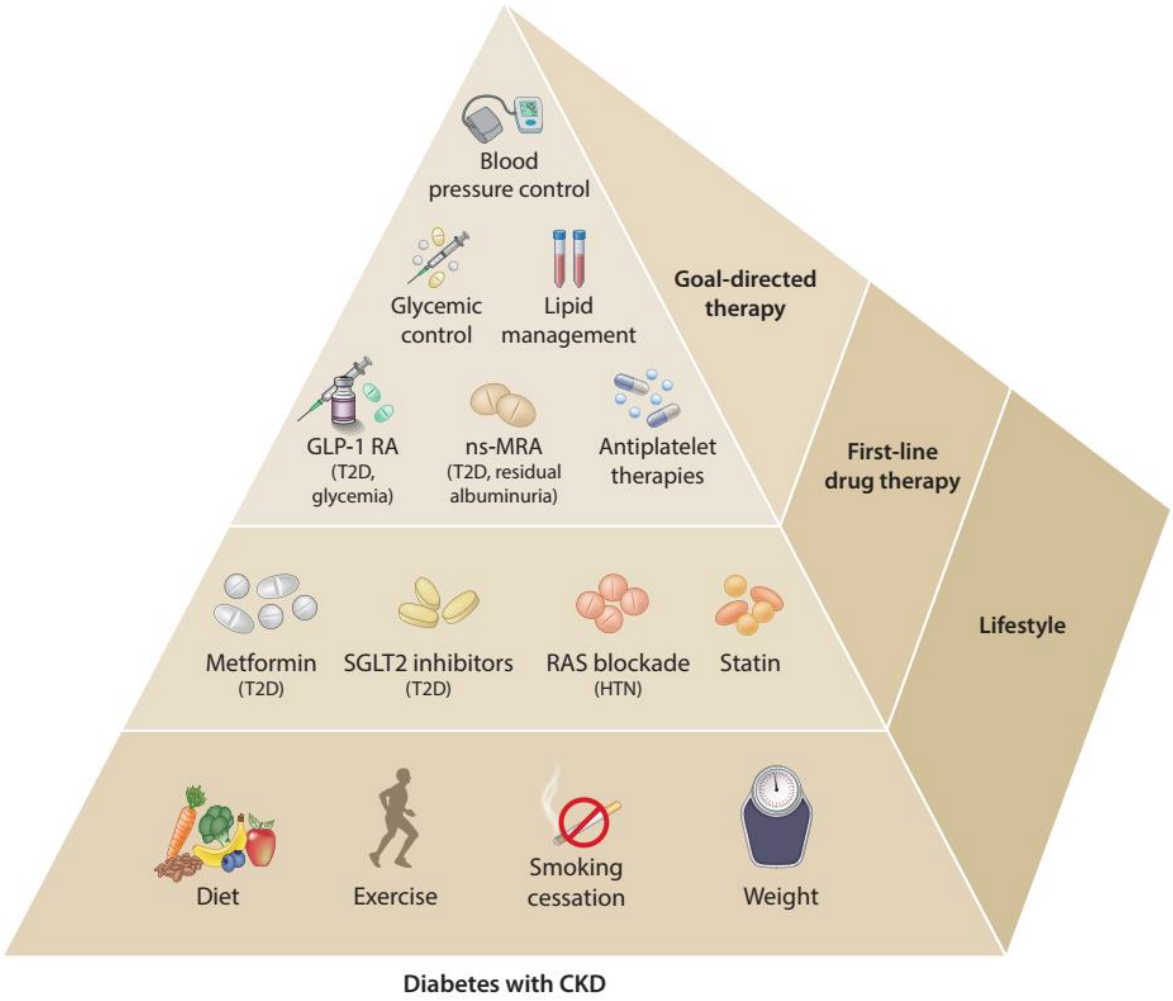
SUMMARY OF RECOMMENDATION STATEMENTS AND PRACTICE POINTS

Chapter 1: Comprehensive care in patients with diabetes and CKD

1.1 Comprehensive diabetes and CKD management

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figures 1 and 2).

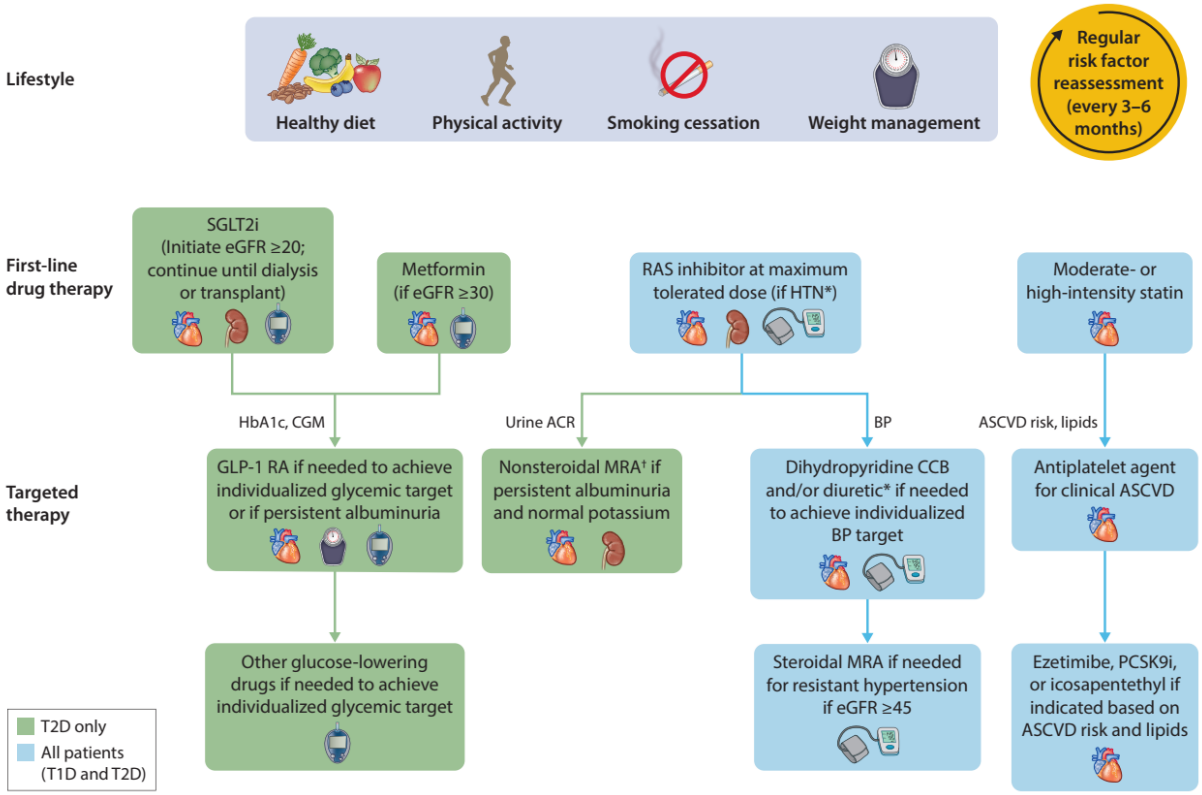
Figure 1. Kidney-heart risk factor management



Glycemic control is based on insulin for type 1 diabetes and a combination of metformin and SGLT2 inhibitors (SGLT2i) for type 2 diabetes. Metformin may be given when eGFR ≥30 ml/min per 1.73 m^2 and SGLT2i should be used when eGFR is ≥20 ml/min per 1.73 m^2. SGLT2i are recommended for patients with type 2 diabetes and chronic kidney disease (CKD). Renin–angiotensin system (RAS) inhibition is recommended for patients with albuminuria and hypertension. Aspirin generally should be used lifelong for secondary prevention among those with established cardiovascular disease and may be considered for

primary prevention among high-risk individuals, with dual antiplatelet therapy used in patients after acute coronary syndrome or percutaneous coronary intervention. RAS, renin-angiotensin system; SGLT2, sodium–glucose cotransporter-2

*Figure 2. Holistic approach for improving outcomes in patients with diabetes and CKD**


Lifestyle
Healthy diet
Physical activity
Smoking cessation
Weight management
Regular risk factor reassessment (every 3–6 months)
First-line drug therapy
SGLT2i (Initiate eGFR ≥20; continue until dialysis or transplant)
Metformin (if eGFR ≥30)
RAS inhibitor at maximum tolerated dose (if HTN*)
Moderate- or high-intensity statin
HbA1c, CGM
Urine ACR
BP
ASCVD risk, lipids
Targeted therapy
GLP-1 RA if needed to achieve individualized glycemic target or if persistent albuminuria
Nonsteroidal MRA† if persistent albuminuria and normal potassium
Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP target
Antiplatelet agent for clinical ASCVD
Other glucose-lowering drugs if needed to achieve individualized glycemic target
Steroidal MRA if needed for resistant hypertension if eGFR ≥45
Ezetimibe, PCSK9i, or icosapentethyl if indicated based on ASCVD risk and lipids
T2D only
All patients (T1D and T2D)

*ACEi or ARB should be first-line therapy for hypertension when albuminuria is present, otherwise dihydropyridine CCB or diuretic can also be considered; all three classes often needed to attain BP targets.
†Finerenone is currently the only nonsteroidal MRA with proven clinical kidney and cardiovascular benefits.
ACE, angiotensin-converting enzyme inhibitor; ACR, albumin-creatinine ratio; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CGM, continuous glucose monitoring; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MRA, mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SGLT2, sodium-glucose cotransporter-2; T2D, Type 2 diabetes; TG, triglycerides

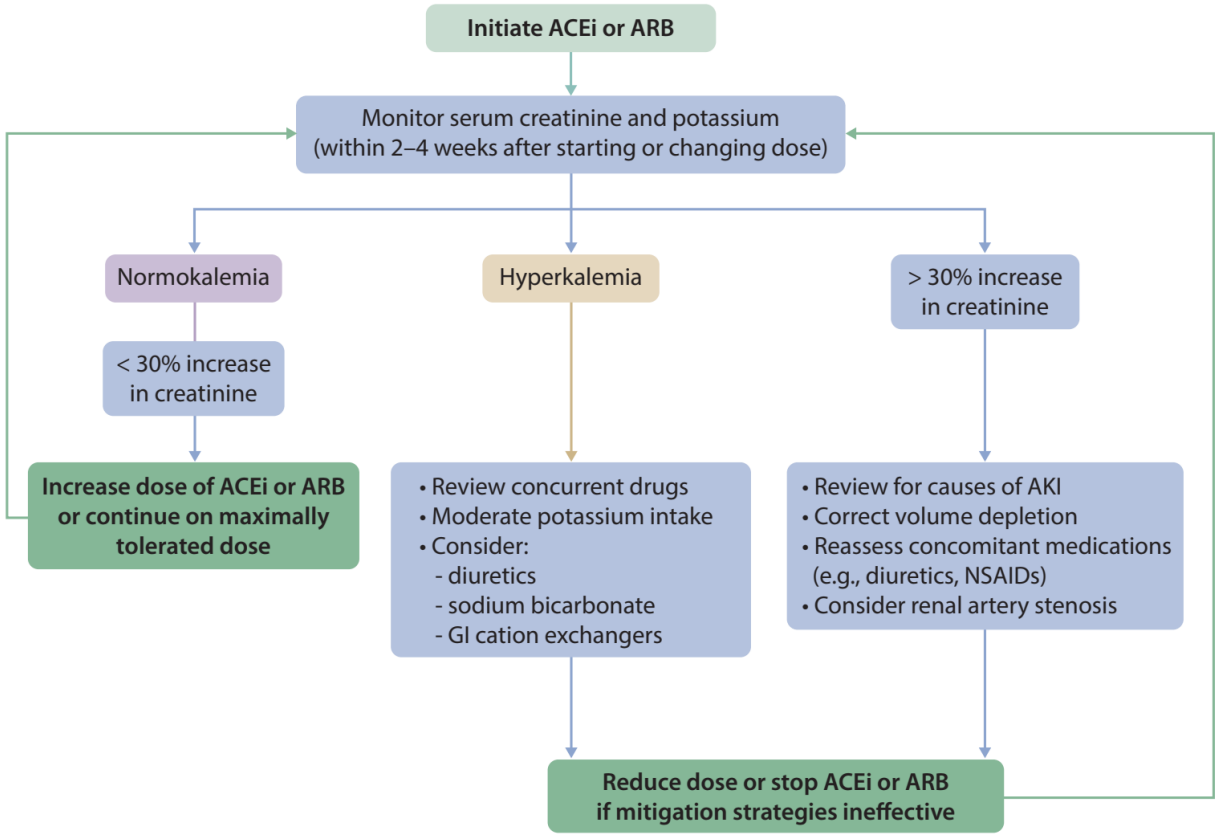
1.2 Renin-angiotensin system (RAS) blockade

Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated (1B).

Practice Point 1.2.1: For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.

Practice Point 1.2.2: Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2–4 weeks of initiation or increase in the dose of an ACEi or ARB (Figure 4).

Figure 4. Monitoring of serum creatinine and potassium during ACEi or ARB treatment – dose adjustment and monitoring of side effects


Initiate ACEi or ARB
Monitor serum creatinine and potassium (within 2–4 weeks after starting or changing dose)
Normokalemia
Hyperkalemia
> 30% increase in creatinine
< 30% increase in creatinine
Increase dose of ACEi or ARB or continue on maximally tolerated dose
• Review concurrent drugs
• Moderate potassium intake
• Consider:
- diuretics
- sodium bicarbonate
- GI cation exchangers
• Review for causes of AKI
• Correct volume depletion
• Reassess concomitant medications (e.g., diuretics, NSAIDs)
• Consider renal artery stenosis
Reduce dose or stop ACEi or ARB if mitigation strategies ineffective

ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Practice Point 1.2.3: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose (Figure 4).

Practice Point 1.2.4: Advise contraception in women who are receiving ACEi or ARB therapy and discontinue these agents in women who are considering pregnancy or who become pregnant.

Practice Point 1.2.5: Hyperkalemia associated with the use of an ACEi or ARB can often be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping ACEi or ARB immediately (Figure 4).

Practice Point 1.2.6: Reduce the dose or discontinue ACEi or ARB therapy in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite the medical treatment outlined in Practice Point 1.2.5, or to reduce uremic symptoms while treating kidney failure (eGFR <15 ml/min per 1.73 m^2).

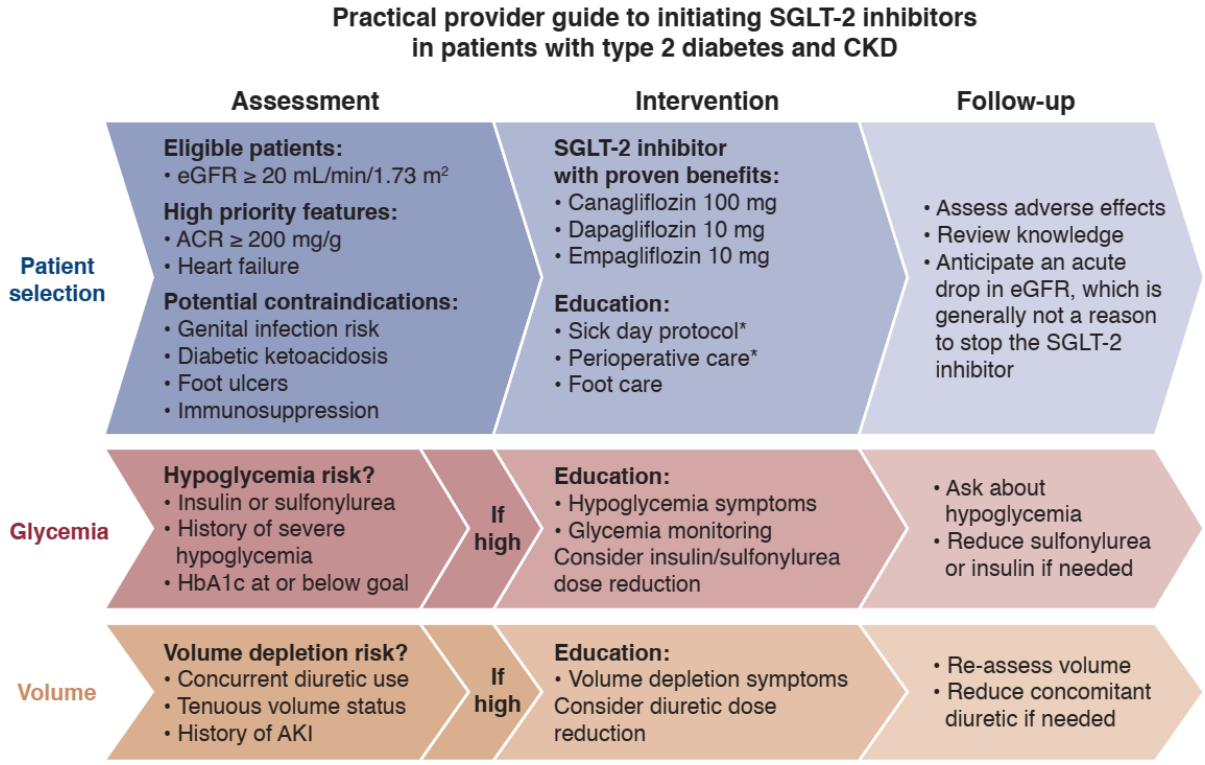
Practice Point 1.2.7: Use only one agent at a time to block the RAS. The combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.

1.3 Sodium–glucose cotransporter-2 inhibitors (SGLT2i)

Recommendation 1.3.1: We recommend treating patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i (1A).

Practice Point 1.3.1: The recommendation for SGLT2i is for kidney and cardiovascular protection and has been shown to have safety and benefit in CKD patients, even for those without T2D. Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to current treatment regimen (Figure 6).

Figure 6. Practical approach to initiating sodium-glucose transport protein 2 inhibitors (SGLT2i) in patients with T2D and CKD



*Sick day protocol (for illness or excessive exercise or alcohol intake): temporarily withhold sodium-glucose cotransporter 2 inhibitor (SGLT2i), keep drinking and eating (if possible), check blood glucose and blood ketone levels more often, and seek medical help early. Periprocedural/perioperative care: inform patients about risk of diabetic ketoacidosis, withhold SGLT2i the day of day-stay procedures and limit fasting to minimum required, withhold SGLT2i at least 2 days in advance and the day of procedures/surgery requiring one or more days in hospital and/or bowel preparation (which may require increasing other glucose-lowering drugs during that time), measure both blood glucose and blood ketone levels on hospital admission (proceed with procedure/surgery if the patient is clinically well and ketones are, 1.0 mmol/l), and restart SGLT2i after procedure/surgery only when eating and drinking normally. HbA1c, hemoglobin A1c; ACR, albumin-creatinine ratio.

Practice Point 1.3.2: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Practice Point 1.3.3: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

Practice Point 1.3.4: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

Practice Point 1.3.5: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

Practice Point 1.3.6: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.

Practice Point 1.3.7: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 1.3.1).

1.4 Mineralocorticoid receptor antagonists (MRA)

Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min/1.73 m^2, normal serum potassium concentration, and albuminuria despite maximum tolerated dose of RAS inhibitor. (2A)

Practice Point 1.4.1: Nonsteroidal MRAs are most appropriate for patients with T2D who are at high risks of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard of care therapies.

Practice Point 1.4.2. In general, SGLT2i should be initiated prior to adding a nonsteroidal MRA for treatment of T2D and CKD.

Practice Point 1.4.3. To mitigate risk of hyperkalemia, select patients with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA.

Practice Point 1.4.4. The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

Practice Point 1.4.5. A steroidal MRA should be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low GFR.

1.5 Smoking cessation

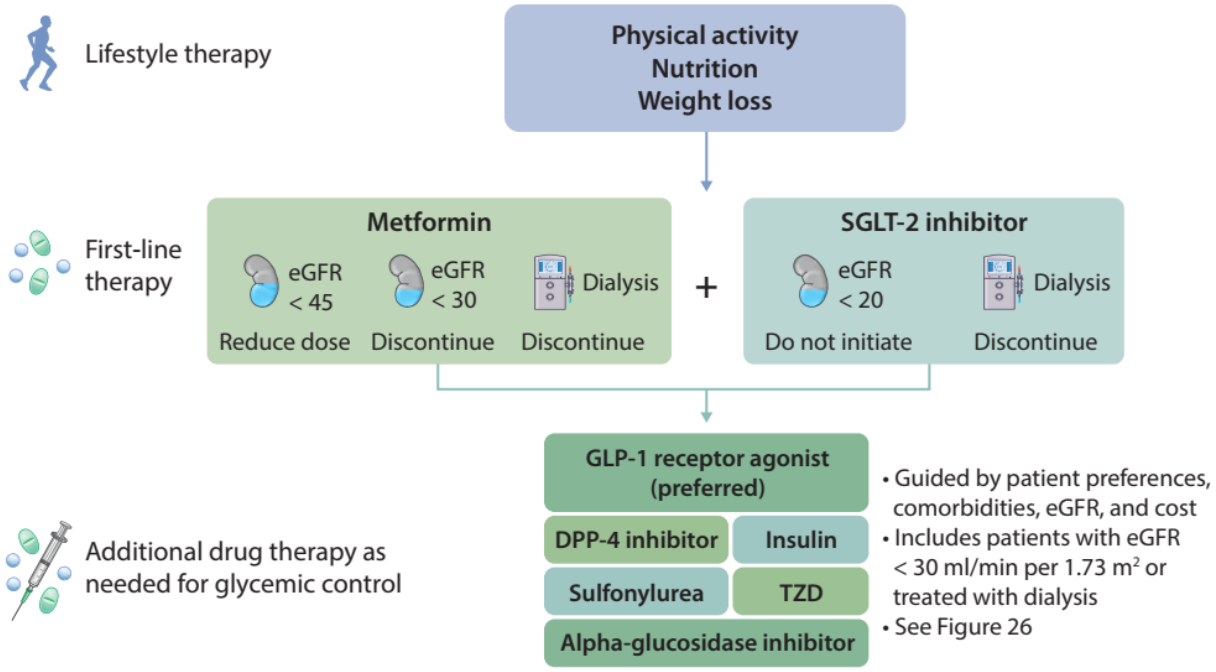
Recommendation 1.5.1: We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products (1D).

Practice Point 1.5.1: Physicians should counsel patients with diabetes and CKD to reduce secondhand smoke exposure.

Chapter 4: Glucose-lowering therapies in patients with type 2 diabetes (T2D) and CKD

Practice Point 4.1: Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with metformin and a SGLT2i, and additional drug therapy as needed for glycemic control (Figure 23).

Figure 23. Treatment algorithm for selecting glucose-lowering drugs for patients with T2D and CKD

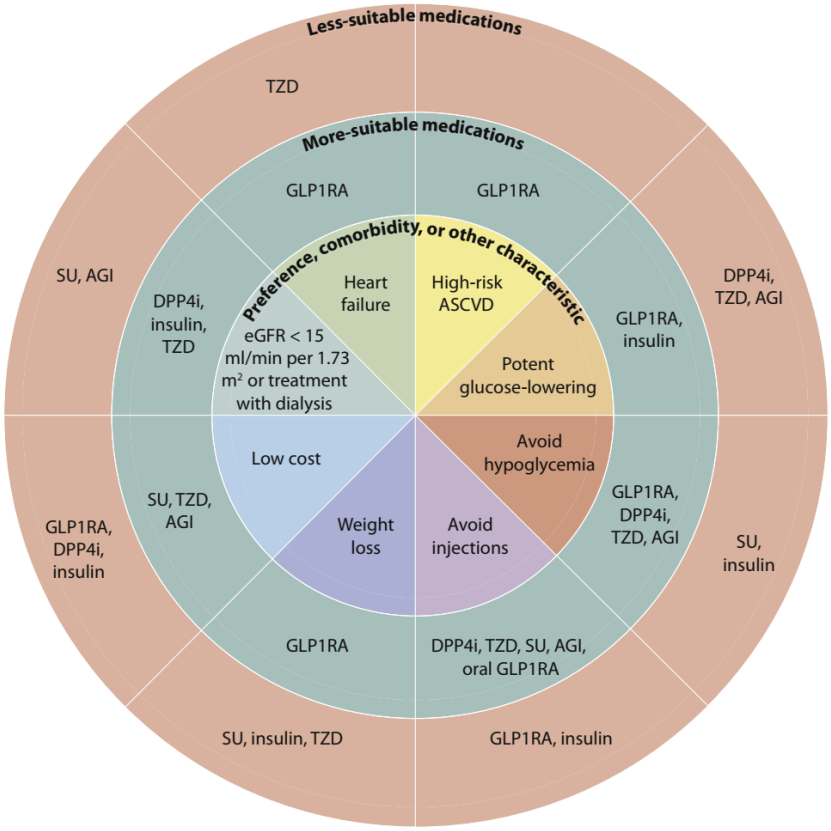


Kidney icon indicates estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2); dialysis machine icon indicates dialysis. CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes; TZD, thiazolidinedione

Practice Point 4.2: Most patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 would benefit from treatment with both metformin and an SGLT2i.

Practice Point 4.3: Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonist (GLP-1 RA) generally preferred (Figure 25).

Figure 25. Patient factors influencing the selection of glucose-lowering drugs other than SGLT2i and metformin in T2D and CKD



AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione

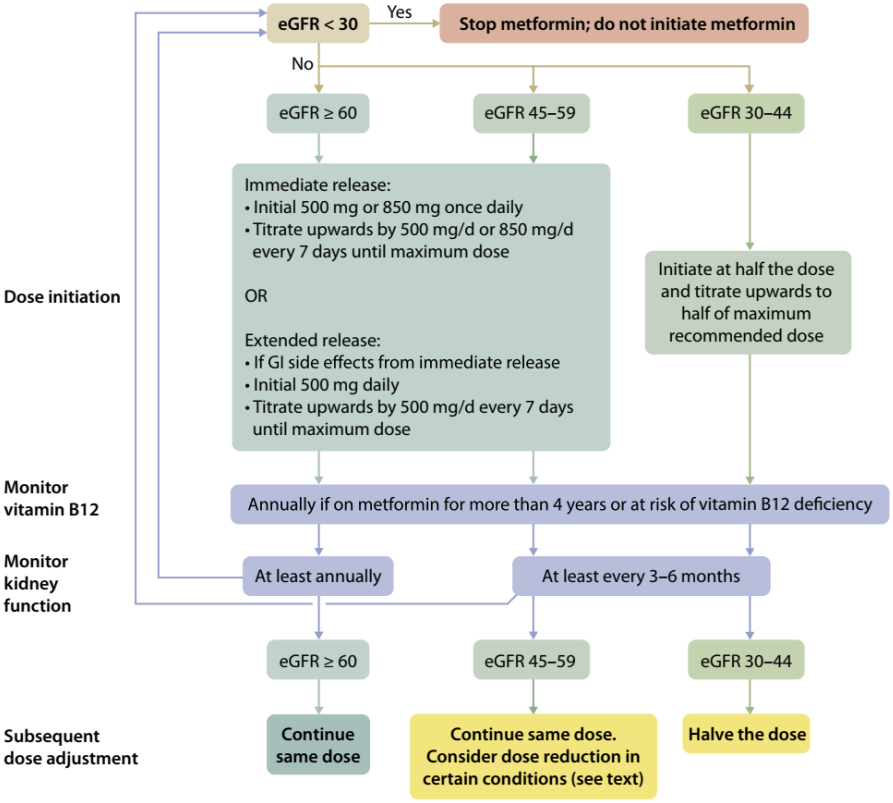
4.1 Metformin

Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 with metformin (1B).

Practice Point 4.1.1: Treat kidney transplant recipients with T2D and an eGFR ≥30 ml/min per 1.73 m^2 with metformin according to recommendations for patients with T2D and CKD.

Practice Point 4.1.2: Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when the eGFR is <60 ml/min per 1.73 m^2 (Figure 27).

Figure 27. Suggested approach in dosing metformin based on the level of kidney function


eGFR < 30
Yes
Stop metformin; do not initiate metformin
No
eGFR ≥ 60
eGFR 45–59
eGFR 30–44
Dose initiation
Immediate release:
• Initial 500 mg or 850 mg once daily
• Titrate upwards by 500 mg/d or 850 mg/d every 7 days until maximum dose
OR
Extended release:
• If GI side effects from immediate release
• Initial 500 mg daily
• Titrate upwards by 500 mg/d every 7 days until maximum dose
Initiate at half the dose and titrate upwards to half of maximum recommended dose
Monitor vitamin B12
Annually if on metformin for more than 4 years or at risk of vitamin B12 deficiency
Monitor kidney function
At least annually
At least every 3–6 months
eGFR ≥ 60
eGFR 45–59
eGFR 30–44
Subsequent dose adjustment
Continue same dose
Continue same dose. Consider dose reduction in certain conditions (see text)
Halve the dose

eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m^2); GI, gastrointestinal

Practice Point 4.1.3: Adjust the dose of metformin when the eGFR is <45 ml/min per 1.73 m^2, and for some patients when the eGFR is 45–59 ml/min per 1.73 m^2 (Figure 27).

Practice Point 4.1.4: Monitor patients for vitamin B12 deficiency when they are treated with metformin for more than 4 years.

4.2 Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

Recommendation 4.2.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (1B).

Practice Point 4.2.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

Practice Point 4.2.2: To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly (Figure 29).

Figure 29. Dosing for available GLP-1 RA and dose modification for CKD

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with CrCl >30 ml/min
Liraglutide	0.6 mg, 1.2 mg, and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist

Practice Point 4.2.3: GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.

Practice Point 4.2.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA is used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.

Practice Point 4.2.5. GLP-1 RA may be preferentially used in patients with obesity, T2D, and CKD to promote intentional weight loss.

Chapter 1: Comprehensive care in patients with diabetes and CKD

1.1 Comprehensive diabetes and CKD management

Optimal management of CKD in diabetes is a complex, multidisciplinary, cross-functional team effort. It bridges from diabetes management in general practice or diabetology settings to CKD management in the nephrology setting. Since multi-morbidity is common among people with diabetes and CKD, care usually involves many other specialties, including but not limited to ophthalmology, neurology, orthopedic surgery, and cardiology. With the patient at the center, the team includes medical doctors, nurses, dietitians, educators, lab technicians, podiatrists, family members, and potentially many others depending on local organization and structure. In this guideline, the background and organization of this chronic care model are described in Section 5.2: Team-based integrated care.

Structured education is critical to engage people with diabetes and CKD to self-manage their disease and participate in the necessary shared decision-making regarding the management plan. Several models have been proposed, as outlined in Chapter 5. It is essential that education is structured, monitored, individualized, and evaluated in order for it to be effective.

Individuals with diabetes and CKD are at risk for acute diabetes-related complications such as hypoglycemia and diabetic ketoacidosis; long-term complications such as retinopathy, neuropathy, and foot complications; the risk of kidney failure with a need for dialysis or transplantation; and in particular, the risk of cardiovascular complications, including ischemia, arrhythmia, and heart failure. Comprehensive diabetes care, therefore, includes regular screening for these complications and management of the many cardiovascular risk factors in addition to hyperglycemia, such as hypertension, dyslipidemia, obesity, and lifestyle factors, including diet, smoking, and physical activity.

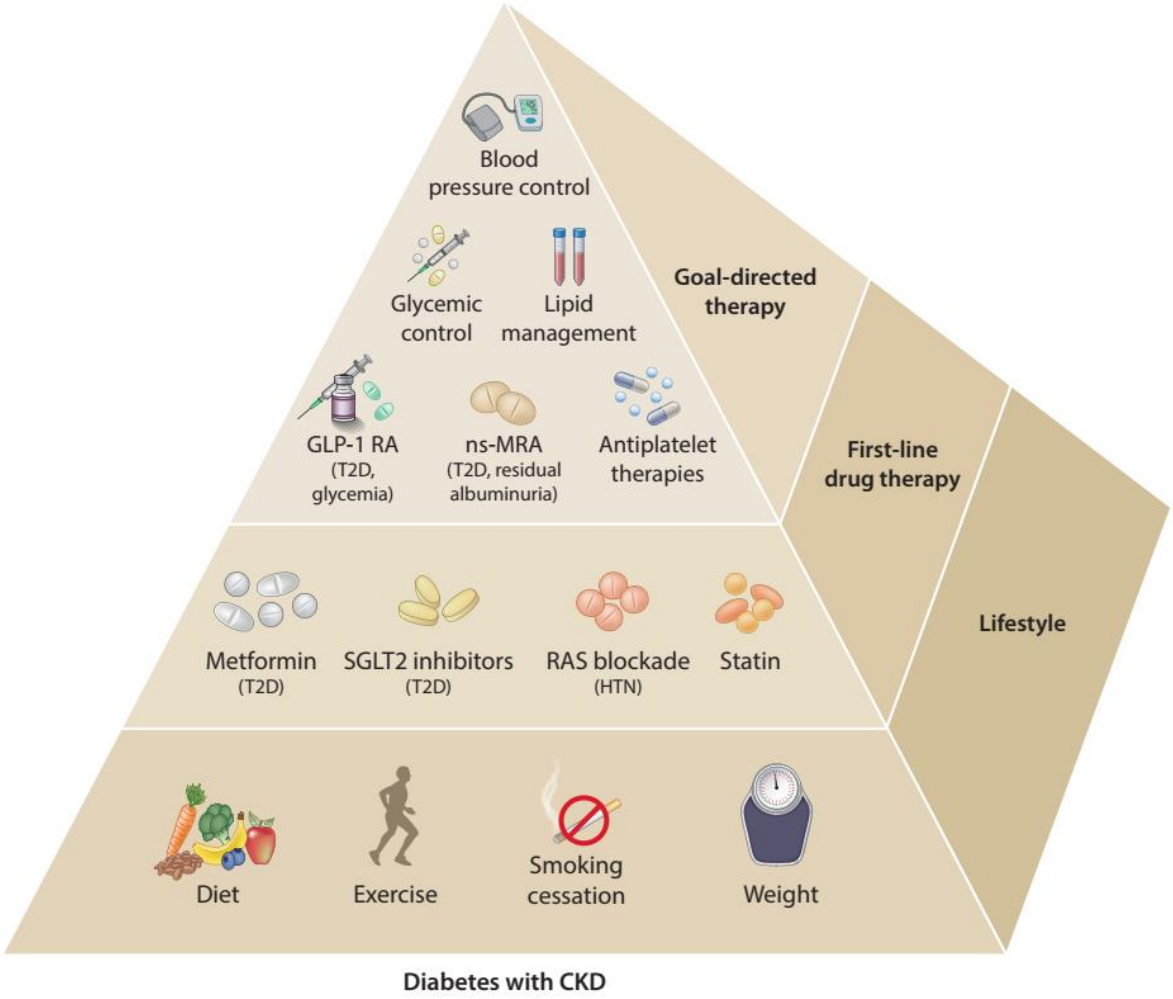
Aspirin generally should be used lifelong for secondary prevention among those with established cardiovascular disease (CVD),[1] with dual antiplatelet therapy used in patients after acute coronary syndrome or percutaneous coronary intervention as per clinical guidelines.[2] Aspirin may be considered for primary prevention among high-risk individuals,[1] but it should be balanced against an increased risk for bleeding including thrombocytopathy with low GFR.[3] Although the risk for thrombotic and embolic events is high, the optimal antiplatelet and antithrombotic therapy in diabetes and CKD has not been well-studied.[4]

The prognosis in an observational study of T2D in Sweden demonstrated how cardiovascular risk and mortality is dependent on the number of uncontrolled risk factors.[5] Multifactorial intervention is needed to target these risk factors with lifestyle modification, including smoking cessation support, dietary counseling, physical activity, and pharmacologic intervention. Multifactorial intervention in T2D reduced the onset and progression of diabetic kidney disease compared to currently recommended care.[6] In addition, studies in people with T2D and early CKD demonstrated the long-term benefit of multifactorial intervention on the development of microvascular and macrovascular complications and mortality.[7, 8] Recently we have seen reduction in progression of CKD in T2D with SGLT2i and nonsteroidal mineralocorticoid receptor antagonists (MRAs), as discussed in subsequent sections, as well as with endothelin receptor antagonists. Ongoing trials may offer additional new opportunities.[9]

With multiple effective treatment options now often available to patients, initiation and titration of comprehensive care becomes more complicated. Sequencing of interventions should be individualized to each patient's pressing individual clinical needs. For glycemic management in T2D, most guidelines recommend starting with metformin, while others suggest starting with SGLT2i or GLP-1 RA in patients with CKD or ASCVD, as their organ protective effects are better documented. This guideline recommends that metformin and an SGLT2i generally both be used as first-line treatment of patients with T2D and CKD, when eGFR allows (Figures 1 and 2). In addition, many drugs have hemodynamic effects to reduce intraglomerular pressure, including RASi, SGLT2i, and MRAs. It is logical to institute and

titrate these sequentially, especially for patients with high risk of acute kidney injury due to low eGFR or concurrent use of medications that may contribute to kidney hypoperfusion, such as diuretics. If and when sequencing treatments is required, it is critically important to ensure that all effective and indicated treatments are implemented in an expeditious manner to maximize benefits. To accomplish this, frequent contacts may be needed and multidisciplinary team care can be essential, as outlined in Chapter 5.2.

Figure 1. Kidney-heart risk factor management



Glycemic control is based on insulin for type 1 diabetes and a combination of metformin and SGLT2 inhibitors (SGLT2i) for type 2 diabetes. Metformin may be given when eGFR ≥30 ml/min per 1.73 m^2 and SGLT2i should be used when eGFR is ≥20 ml/min per 1.73 m^2. SGLT2i are recommended for patients with type 2 diabetes and chronic kidney disease (CKD). Renin–angiotensin system (RAS) inhibition is recommended for patients with albuminuria and hypertension. Aspirin generally should be used lifelong for secondary prevention among those with established cardiovascular disease and may be considered for primary prevention among high-risk individuals, with dual antiplatelet therapy used in patients after acute coronary syndrome or percutaneous coronary intervention. RAS, renin-angiotensin system; SGLT2, sodium–glucose cotransporter-2

This guideline focuses on selected topics for which evidence-based guidance can be provided; it does not cover topics like blood pressure and lipid management as these are dealt with in other KDIGO guidelines. However, management of CKD in diabetes requires multifactorial risk factor control, including targeting all of the risk factors mentioned above and also indicated in Figure 1 and 2.

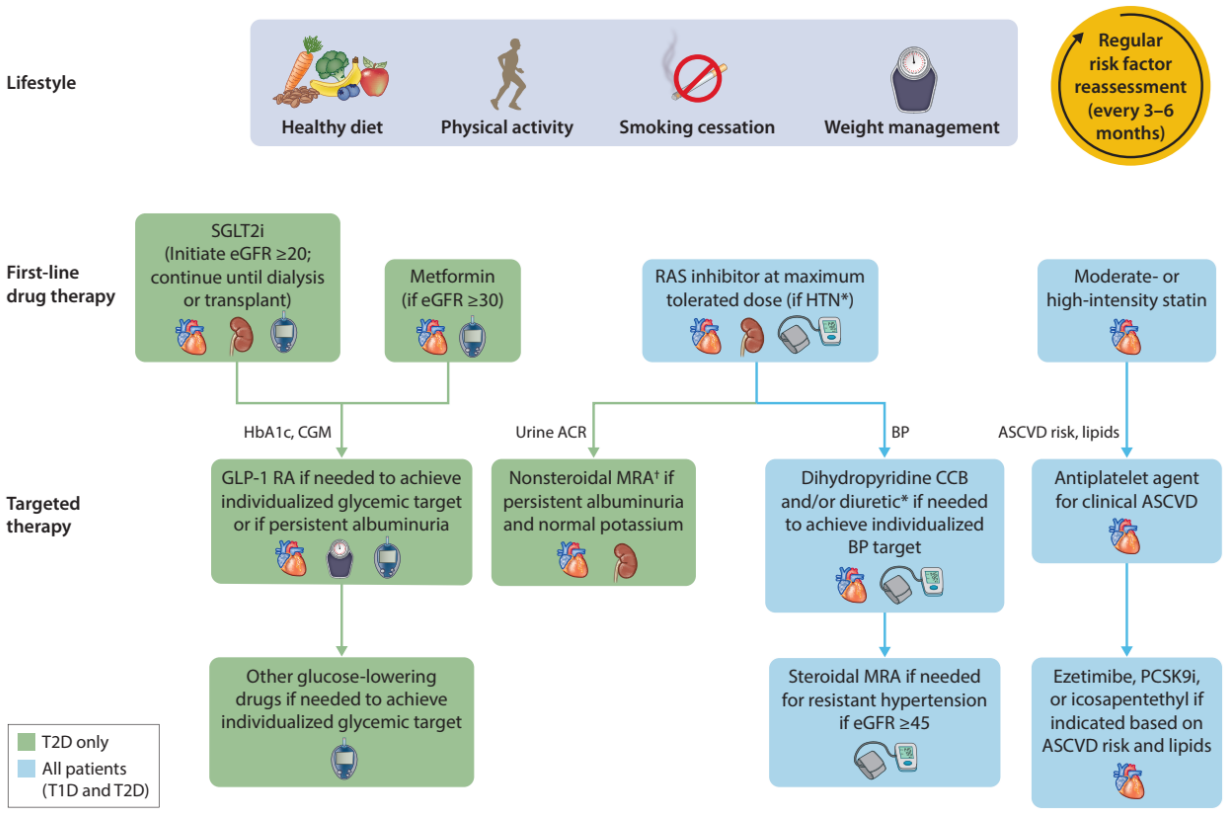
Overall, the guideline is designed to apply to a broad population of patients with diabetes and CKD. T1D and T2D are both addressed, with differences in approach to management highlighted as appropriate.

Pharmacologic management of glycemia is one aspect of care that differs substantially by diabetes type, but also, the benefits of SGLT2 inhibitors and nonsteroidal MRAs have been demonstrated only in T2D with CKD. The GLP-1 RAs are as well tested only in the T2D population. There is a substantial difference in the evidence base; thus, this guideline includes evidence-based recommendations for pharmacologic glucose-lowering treatment in T2D and CKD. However, it defers pharmacologic glucose-lowering treatment of T1D, based on insulin, to existing guidelines from diabetes organizations. Similarly, the Work Group addressed care for patients with all severities of CKD, patients with a kidney transplant, and patients treated with hemodialysis or peritoneal dialysis. CKD is defined as persistently elevated urine albumin excretion (≥30 mg/g [3 mg/mmol] creatinine), persistently reduced eGFR (eGFR <60 ml/min per 1.73 m^2), or both, for more than 3 months, in accordance with current KDIGO guidelines.

Practice Point 1.1.1: Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease (Figures 1 and 2).

As kidney function deteriorates and reaches lower GFR, changes to types and doses of medications often need to be adjusted. In addition, management of anemia, bone and mineral disorders, fluid and electrolyte disturbances, and eventually dialysis and transplantation become increasingly dominant. As other KDIGO guidelines cover these latter topics, they are not addressed in the current guideline. However, to the extent possible, guidance is provided in relation to the selected topics, particularly diabetes monitoring, glycemia management, and RAS blockade, as well as lifestyle factors for all CKD severities.

*Figure 2. Holistic approach for improving outcomes in patients with diabetes and CKD**


Lifestyle
Healthy diet
Physical activity
Smoking cessation
Weight management
Regular risk factor reassessment (every 3–6 months)
First-line drug therapy
SGLT2i (Initiate eGFR ≥20; continue until dialysis or transplant)
Metformin (if eGFR ≥30)
RAS inhibitor at maximum tolerated dose (if HTN*)
Moderate- or high-intensity statin
HbA1c, CGM
Urine ACR
BP
ASCVD risk, lipids
Targeted therapy
GLP-1 RA if needed to achieve individualized glycemic target or if persistent albuminuria
Nonsteroidal MRA† if persistent albuminuria and normal potassium
Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP target
Antiplatelet agent for clinical ASCVD
Other glucose-lowering drugs if needed to achieve individualized glycemic target
Steroidal MRA if needed for resistant hypertension if eGFR ≥45
Ezetimibe, PCSK9i, or icosapentethyl if indicated based on ASCVD risk and lipids
T2D only
All patients (T1D and T2D)

*ACEi or ARB should be first-line therapy for hypertension when albuminuria is present, otherwise dihydropyridine CCB or diuretic can also be considered; all three classes often needed to attain BP targets.

[†]Finerenone is currently the only nonsteroidal MRA with proven clinical kidney and cardiovascular benefits.
ACE, angiotensin-converting enzyme inhibitor; ACR, albumin-creatinine ratio; ARB, angiotensin II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CCB, calcium channel blocker; CGM, continuous glucose monitoring; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MRA, mineralocorticoid receptor antagonist; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SGLT2, sodium-glucose cotransporter-2; T2D, Type 2 diabetes; TG, triglycerides

Research recommendations

- Additional trials to prevent CKD progression and CVD are needed. addressing how best to combine lifestyle factors and the multiple new therapies (such as SGLT2i and MRAs) compared to standard of care
- To study how best to initiate, combine, and titrate the different treatment options being part of the comprehensive care.
- The benefit of new therapies and multifactorial intervention should be tested in broader populations with CKD and diabetes including type 1 diabetes, dialysis and kidney transplant treated patients.
- Studies should evaluate the concept of precision medicine in diabetes and CKD. Should all have the same comprehensive care, or should it rather be tailored medicine to the individual CKD/diabetes type and risk profile?
- Implementation science research to improve dissemination and implementation of evidence-based therapies.

1.2 Renin-angiotensin system (RAS) blockade

Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated (1B).

This recommendation places a high value on the potential benefits of RAS blockade with ACEi or ARBs for slowing the progression of CKD in patients with diabetes, while it places a relatively lower value on the side effects of these drugs and the need to monitor kidney function and serum potassium.

Key information

Balance of benefits and harms

Moderately or severely increased albuminuria is related to increased kidney and cardiovascular risk compared to normal albumin excretion. The Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria 2 (IRMA-2)[10] and The Incipient to Overt: Angiotensin II Blocker, Telmisartan,

Investigation on Type 2 Diabetic Nephropathy (INNOVATION)[11] studies were placebo-controlled trials enrolling patients with T2D and moderately increased albuminuria (30–300 mg/g [3–30 mg/mmol]). They were designed to determine whether RAS blockade reduced the risk of progression and CKD in diabetes, defined as the development of severely increased albuminuria (>300 mg/g [30 mg/mmol]). The IRMA-2 study showed that treatment with irbesartan, an ARB, was associated with a dose-dependent reduction in the risk of progression of CKD, with an almost 3-fold risk reduction with the highest dose (300 mg per day) at 2 years of follow-up.[10] This effect was independent of the blood pressure–lowering properties of irbesartan. In the INNOVATION trial, the ARB telmisartan was associated with a lower transition rate to overt nephropathy than placebo after 1 year of follow-up.[11] In this trial, telmisartan also significantly reduced blood pressure levels. However, after adjustment for the difference in blood pressure levels between the placebo and treatment groups, the beneficial effect of telmisartan in delaying progression to overt nephropathy persisted.

Furthermore, the beneficial effects of RAS blockade were shown to extend to patients with severely increased albuminuria. Two landmark trials, the Irbesartan Diabetic Nephropathy (IDNT)[12] and the Reduction of Endpoints in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (RENAAL)[13] studies, were conducted in patients with T2D and CKD, having albuminuria greater than 1 g/d. In the IDNT trial, treatment with irbesartan compared with placebo resulted in a 33% decrease in the risk of doubling of serum creatinine concentration and was associated with a nonsignificant reduction in the incidence of kidney failure, which was independent of blood pressure. In the RENAAL trial, losartan significantly reduced the incidence of doubling of serum creatinine, kidney failure, and death, each by 16% compared with placebo, in combination with "conventional" antihypertensive treatment. The renoprotective effect conferred by losartan also exceeded the effect attributable to the small differences in blood pressure between the treatment groups.

Consequently, an update to a Cochrane systematic review[14] performed by the ERT concurred that the use of ACEi or ARB treatment in patients with diabetes and CKD was associated with a reduction in the progression of CKD with regard to the development of severely increased albuminuria (relative risk [RR]: 0.45; 95% confidence interval [CI]: 0.29–0.69 and RR: 0.45; 95% CI: 0.35–0.57, respectively) or doubling of serum creatinine (RR: 0.68; 95% CI: 0.47–1.00 and RR: 0.84; 95% CI: 0.72–0.98, respectively) (Supplementary Tables S4[15-44] and S5[12, 32, 37, 45-49]).

ACEi and ARBs are generally well-tolerated. The systematic reviews performed suggested that ACEi and ARB treatment may cause little or no difference in the occurrence of serious adverse events. However, angioedema has been associated with the use of ACEi, with a weighted incidence of 0.30% (95% CI: 0.28–0.32) reported in one systematic review.[50] Dry cough is also a known adverse effect of ACEi treatment. It has been postulated that angioedema and cough are due to the inhibition of ACE-dependent degradation of bradykinin, and a consideration can be made to switch affected patients to an ARB, with which the incidence of angioedema is not significantly different from that of placebo (ARB: 0.11%; 95% CI: 0.09–0.13 vs. placebo: 0.07%; 95% CI: 0.05–0.09).

Similar dose dependency of the albuminuria-lowering effect, as described for IRMA-2, has been demonstrated in several studies with ACEi and ARB treatments, but the side effects increase with increasing doses. Thus, initiation should begin at a low dose with up-titration to the highest approved dose the patient can tolerate. *Post hoc* analysis of randomized trials and observational cohorts have demonstrated that an initial larger albuminuria reduction is associated with better long-term outcomes.[51, 52]

Quality of the evidence

The overall quality of the evidence was rated as moderate. From randomized controlled trials (RCTs) that compared an ACEi with placebo/standard, the quality of the evidence for critical outcomes, such as all-cause mortality, moderately increased to severely increased albuminuria progression, and doubling

serum creatinine, was moderate (Supplementary Table S4). Additionally, in RCTs that compared ARB with placebo/standard of care, the quality of the evidence was moderate for these critical outcomes (Supplementary Table S5). In both comparisons, the quality of the evidence was initially downgraded to moderate because of serious study limitations, with unclear allocation concealment across the studies. Other outcomes, such as cardiovascular mortality, cardiovascular events, and serious adverse events, were sparingly reported in these studies. The imprecision, in addition to study limitations, downgraded the quality of the evidence for these outcomes to low. The overall quality of the evidence has been driven by the critical outcomes of the doubling of serum creatinine level and albuminuria progression, and not by the cardiovascular outcomes or adverse events because of the lack of reporting of these outcomes in trials.

Values and preferences

The progression of CKD to kidney failure, the avoidance or delay in initiating dialysis therapy, and the antecedent risks associated with dialysis were judged to be critically important to patients. In addition, the side effects with ACEi or ARB therapy, and the need for monitoring of blood pressure, serum creatinine, and potassium, were judged to be important and acceptable to the majority of patients. The Work Group, therefore, judged that most, if not all, patients would choose to receive RAS blockade treatment with either an ACEi or ARB for kidney protection effects, compared to receiving no treatment. This recommendation applies to both T1D and T2D, as well as kidney transplant recipients; however, this recommendation does not apply to patients on dialysis.

The evidence does not demonstrate superior efficacy of ACEi over ARB treatment or vice versa, and the choice between these 2 drug classes will depend on other factors, including patient preferences, cost, availability of generic formulations, and side-effects profiles of individual drugs. ACEi-induced cough is the predominant cause of intolerance to this class of drug, affecting about 10% of patients.[53] In clinical practice, affected patients are often switched to an ARB so as not to lose the renoprotective effects of RAS blockade, although the improvement in tolerability has not been evaluated in an RCT.

Resources and other costs

Generic formulations of both ACEi and ARBs are widely available at low cost in many parts of the world. Moreover, both have been included in the World Health Organization (WHO) list of essential medicines.[54]

Considerations for implementation

ACEi and ARBs are potent medications and can cause hypotension, hyperkalemia, and a rise in serum creatinine level. The inhibition of aldosterone action and its effect on efferent arteriole dilatation could result in hyperkalemia and a rise in serum creatinine level in patients with renal artery stenosis. Consequently, blood pressure, serum potassium, and serum creatinine should be monitored in patients who are started on RAS blockade or whenever there is a change in the dose of the drug. The changes in blood pressure, potassium, and kidney function are usually reversible if medication is stopped or doses are reduced.

Figure 3 outlines the common types of ACEi and ARBs available and the respective recommended starting and maximum doses based on their blood pressure–lowering effects, including the need for dose adjustment with decline in kidney function. This is only a suggested guide, and formulations and doses may differ among different regulatory authorities.

The use of ACEi and ARB treatment has been associated with an increased risk of adverse effects to the fetus during pregnancy. Women who are planning for pregnancy or who are pregnant while on RAS blockade treatment should have the drug discontinued (see Practice Point 1.2.4).

Figure 3. Different formulations on ACEi and ARB

Drug		Starting dose	Maximum daily dose	Kidney impairment
ACE inhibitors	Benazepril	10 mg once daily	80 mg	CrCl ≥ 30 ml/min: No dosage adjustment needed. CrCl < 30 ml/min: Reduce initial dose to 5 mg PO once daily for adults. Parent compound not removed by hemodialysis
	Captopril	12.5 mg to 25 mg 2 to 3 times daily	Usually 50 mg 3 times daily (may go up to 450 mg/day)	Half-life is increased in patients with kidney impairment CrCl 10–50 ml/min: administer 75% of normal dose every 12–18 hours. CrCl <10 ml/min: administer 50% of normal dose every 24 hours. Hemodialysis: administer after dialysis. About 40% of drug is removed by hemodialysis
	Enalapril	5 mg once daily	40 mg	CrCl ≤ 30 ml/min: In adult patients, reduce initial dose to 2.5 mg PO once daily 2.5 mg PO after hemodialysis on dialysis days; dosage on nondialysis days should be adjusted based on clinical response.
	Fosinopril	10 mg once daily	80 mg	No dosage adjustment necessary Poorly removed by hemodialysis
	Lisinopril	10 mg once daily	40 mg	CrCl 10–30 ml/min: Reduce initial recommended dose by 50% for adults. Max: 40 mg/d CrCl < 10 ml/min: Reduce initial dosage to 2.5 mg PO once daily. Max: 40 mg/d
	Perindopril	2 mg once daily	8 mg	Use is not recommended when CrCl <30 ml/min Perindopril and its metabolites are removed by hemodialysis
	Quinapril	10 mg once daily	80 mg	CrCl 61–89 ml/min: start at 10 mg once daily CrCl 30–60 ml/min: start at 5 mg once daily CrCl 10–29 ml/min: start at 2.5 mg once daily CrCl <10 ml/min: insufficient data for dosage recommendation About 12% of parent compound removed by hemodialysis
	Ramipril	2.5 mg once daily	20 mg	Administer 25% of normal dose when CrCl <40 ml/min Minimally removed by hemodialysis
	Trandolapril	1 mg once daily	4 mg	CrCl <30 ml/min: reduce initial dose to 0.5 mg/d
Angiotensin receptor blockers	Azilsartan	20–80 mg once daily	80 mg	Dose adjustment is not required in patients with mild-to-severe kidney impairment or kidney failure
	Candesartan	16 mg once daily	32 mg	In patients with CrCl <30 ml/min, AUC and Cmax were approximately doubled with repeated dosing. Not removed by hemodialysis
	Irbesartan	150 mg once daily	300 mg	No dosage adjustment necessary. Not removed by hemodialysis
	Losartan	50 mg once daily	100 mg	No dosage adjustment necessary. Not removed by hemodialysis
	Olmesartan	20 mg once daily	40 mg	AUC is increased 3-fold in patients with CrCl <20 ml/min. No initial dosage adjustment is recommended for patients with moderate to marked kidney impairment (CrCl <40 ml/min). Has not been studied in dialysis patients
	Telmisartan	40 mg once daily	80 mg	No dosage adjustment necessary. Not removed by hemodialysis
	Valsartan	80 mg once daily	320 mg	No dosage adjustment available for CrCl <30 ml/min—to use with caution. Not removed significantly by hemodialysis

Dosage recommendations are obtained from Physician Desk Reference and/or US Food and Drug Administration, which are based on information from package inserts registered in the United States. Dosage recommendations may differ across countries and regulatory authorities. ACEi, angiotensin-converting enzyme inhibitor(s); ARB, angiotensin II receptor blocker; AUC, area under the curve; Cmax, maximum or peak concentration; CrCl, creatinine clearance; GFR, glomerular filtration rate.

Rationale

The presence of albuminuria is associated with an increased risk of progression of CKD and the development of kidney failure in patients with CKD and diabetes. It has also been demonstrated that the degree of albuminuria correlates with the risks for kidney failure and that both ACEi and ARBs have been shown to be effective in the reduction of albuminuria and even reversal of moderately increased albuminuria. It has been documented that the albuminuria-lowering effect is dose-related (but has side effects as well). Thus, for maximal effect, start at a low dose and then up-titrate to the highest tolerated and recommended dose. Notwithstanding their anti-albuminuric effects, improvement in kidney outcomes has been demonstrated in multiple RCTs. In addition, both drugs are well-tolerated, and the benefits of treatment outweigh the inconvenience of needing to monitor kidney function and serum potassium level after initiation or change in the dose of the drug. This recommendation, therefore, places a high value on the moderate-quality evidence demonstrating that RAS blockade with ACEi or ARBs slows the rate of kidney function loss in patients with CKD and diabetes. It places a relatively lower value on the side effects of these drugs and the need to monitor kidney function and serum potassium level.

This is a strong recommendation, as the Work Group judged that the retardation of CKD progression and prevention of kidney failure would be critically important to patients, and the majority, if not all, suitable patients would be willing to start treatment with an ACEi or ARB. The Work Group also judged that a large majority of physicians would be comfortable initiating RAS blockade treatment and titrating it to the maximum approved or tolerated dose because of its benefits in kidney protection, their familiarity with this drug, and its good safety profile.

Practice Point 1.2.1: For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.

The benefits of RAS blockade have been less studied in patients with diabetes and CKD without hypertension. Although the IDNT[12] and IRMA-2[10] studies recruited exclusively patients with T2D and hypertension, a small percentage (3.5%) of patients in the RENAAL trial, and 30.9% (163 of 527) of randomized patients in the INNOVATION study were normotensive, suggesting that use of RAS blockade may be beneficial in patients without hypertension.[11, 13] Moreover, due to the strong correlation between the severity of albuminuria and the risk of kidney failure in this population, and given that RAS blockade reduces the severity of albuminuria, the Work Group judged that ACEi and ARB treatment may be beneficial in patients with diabetes and albuminuria but without hypertension. Available data suggest that ACEi and ARB treatments are not beneficial for patients with neither albuminuria nor elevated blood pressure. In T1D with neither albuminuria nor elevated blood pressure, neither an ACEi nor an ARB either slowed the progression of histologic features of diabetes and CKD or reduced the incidence of albuminuria over 5 years.[36] In T2D with neither albuminuria nor elevated blood pressure (normal or well-treated), moderately increased albuminuria was observed less frequently with an ARB, but cardiovascular events were increased.[55] A review found 6 studies in normoalbuminuric T2D patients showing benefit on albuminuria progression by RAS blockade, but most patients had hypertension.[56]

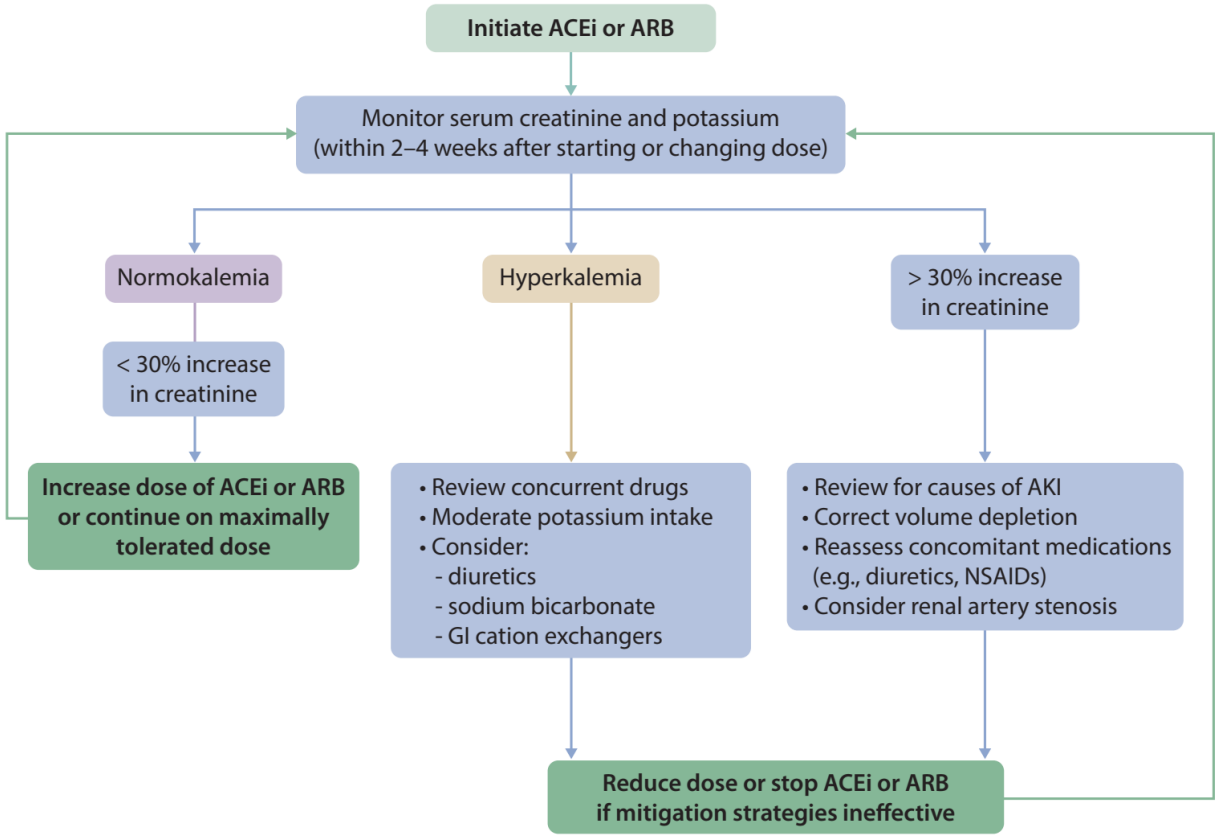
Patients with diabetes and hypertension are at lower risk of CKD progression when urine albumin excretion is normal (<30 mg/g [3 mg/mmol] creatinine), and existing evidence does not demonstrate clear clinical benefit of RAS inhibition for CKD progression in this population. Cardiovascular risk reduction is the most important goal of blood pressure management with normal urine albumin excretion, and multiple classes of antihypertensive agents (including RAS inhibitors, diuretics, and dihydropyridine calcium channel blockers) are appropriate in this setting.

Practice Point 1.2.2: Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2–4 weeks of initiation or increase in the dose of an ACEi or ARB (Figure 4).

ACEi and ARBs are potent antihypertensive agents that counteract the vasoconstrictive effects of angiotensin II. Moreover, blocking the action of angiotensin II causes selectively greater vasodilatation of the efferent arterioles of the glomeruli, resulting in a decline of the intraglomerular pressure, and not unexpectedly, a decrease in the GFR and a rise in serum creatinine level. In addition, RAS blockade inhibits the action of aldosterone, leading to a greater propensity for hyperkalemia. An increase in serum creatinine level, if it occurs, will typically happen during the first 2 weeks of treatment initiation, and it should stabilize within 2–4 weeks in the setting of normal sodium and fluid intake.[57] Therefore, patients should be monitored for symptomatic hypotension, hyperkalemia, and excessive rise in serum creatinine level within 2–4 weeks after initiating or making a change in the dose of the drug, depending on resource availability and patient preferences. Earlier laboratory monitoring (e.g., within 1 week) may be indicated for patients at high risk of hyperkalemia due to low eGFR, history of hyperkalemia, or borderline high serum potassium concentration. Conversely, a longer timing for laboratory monitoring (e.g., after

initiation but not dose titration) may be considered for patients at low risk of hyperkalemia (e.g., patients with normal eGFR and serum potassium level).

Figure 4. Monitoring of serum creatinine and potassium during ACEi or ARB treatment – dose adjustment and monitoring of side effects


Initiate ACEi or ARB
Monitor serum creatinine and potassium (within 2–4 weeks after starting or changing dose)
Normokalemia
Hyperkalemia
> 30% increase in creatinine
< 30% increase in creatinine
Increase dose of ACEi or ARB or continue on maximally tolerated dose
• Review concurrent drugs
• Moderate potassium intake
• Consider:
- diuretics
- sodium bicarbonate
- GI cation exchangers
• Review for causes of AKI
• Correct volume depletion
• Reassess concomitant medications (e.g., diuretics, NSAIDs)
• Consider renal artery stenosis
Reduce dose or stop ACEi or ARB if mitigation strategies ineffective

ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Practice Point 1.2.3: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose (Figure 4).

The rise in serum creatinine level should not be a deterrent in using ACEi or ARB therapy in patients with diabetes and CKD, including those with pre-existing kidney disease.[34] Moreover, there were suggestions in clinical trials that the greatest slowing of kidney disease progression occurred in patients with the lowest eGFR at study initiation.[31, 58] A review of 12 RCTs that evaluated kidney disease progression among patients with pre-existing kidney disease demonstrated a strong association between acute increases of serum creatinine level of up to 30% from baseline that stabilized within 2 months of ACEi therapy initiation and long-term preservation of kidney function.[57]

The most common cause of an acute rise in serum creatinine level following the use of an RAS blockade agent results from a decreased effective arterial blood volume, which often occurs in the setting of volume depletion with aggressive diuretic use and low cardiac output seen in heart failure; or with the use of nonsteroidal anti-inflammatory drugs.[59] In addition, bilateral renal artery stenosis (or stenosis of a single renal artery for patients with a single functioning kidney, including kidney transplant recipients) might also be a cause of elevated serum creatinine level following initiation of RAS blockade treatment, especially in patients with extensive atherosclerotic cardiovascular disease (ASCVD) or who are

smokers.[57] Therefore, in patients with an acute excessive rise in serum creatinine level (>30%), the clinician should evaluate the potential contributing factors highlighted above, sometimes including imaging for bilateral renal artery stenosis aiming to continue ACEi or ARB treatment after these risk factors have been managed.

Practice Point 1.2.4: Advise contraception in women who are receiving ACEi or ARB therapy and discontinue these agents in women who are considering pregnancy or who become pregnant.

The use of drugs that block the RAS is associated with adverse fetal and neonatal effects, especially with exposure during the second and third trimester. The association with exposure during the first trimester, however, is less consistent.

A systematic review of 72 published case reports and case series that included 186 cases of intrauterine exposure to RAS blockade agents found that 48% of newborns exposed to an ACEi, and 87% of those exposed to an ARB, developed complications,[60] with long-term outcomes occurring in 50% of the exposed children. Across exposure to both ACEi and ARBs, the prevalence of neonatal complications was greater with exposure during the second and third trimesters of pregnancy. The most common complications are related to impaired fetal or neonatal kidney function resulting in oligohydramnios during pregnancy and kidney failure after delivery.[61, 62] Other problems include pulmonary hypoplasia, respiratory distress syndrome, persistent patent ductus arteriosus, hypocalvaria, limb defects, cerebral complications, fetal growth restrictions, and miscarriages or perinatal death.[60]

The data regarding first-trimester exposure and the association with fetal or neonatal complications are less consistent. The first possible report of harm came from an epidemiologic evaluation of Medicaid data of 29,507 infants born between 1985 and 2000,[63] which demonstrated that the risks of major congenital malformations, predominantly cardiovascular and neurologic abnormalities, were significantly increased among infants exposed to an ACEi in the first trimester compared to those without exposure to antihypertensive drugs. However, there were other studies that did not demonstrate such an association with ACEi use in the first trimester, after adjusting for underlying disease characteristics, particularly first-trimester hypertension.[64] However, the limitation of most of the studies that showed a negative association with first-trimester exposure is that they did not account for malformations among miscarriages, pregnancy terminations, or stillbirth. Therefore, the possibility of teratogenesis with first-trimester exposure to an ACEi or ARB cannot be confidently refuted, and caution must be undertaken in prescribing these drugs to women of childbearing age.

It is, therefore, the judgment of the Work Group that for women who are considering pregnancy, ACEi and ARB treatment should be avoided. Likewise, women of childbearing age should be counseled appropriately regarding the risks of ACEi and ARB exposure during pregnancy and the need for effective contraception. Women who become pregnant while on RAS blockade treatment should have the drug stopped immediately and be monitored for fetal and neonatal complications.

Practice Point 1.2.5: Hyperkalemia associated with the use of an ACEi or ARB can often be managed by measures to reduce serum potassium levels rather than decreasing the dose or stopping ACEi or ARB immediately (Figure 4).

The cardiovascular and kidney benefits of ACEi and ARB treatment in patients with CKD and diabetes, hypertension, and albuminuria warrant efforts to maintain patients on these drugs, when possible. Hyperkalemia is a known complication with RAS blockade and occurs in up to 10% of outpatients[65] and up to 38% of hospitalized patients[66] receiving an ACEi. Risk factors for the development of hyperkalemia with the use of drugs that inhibit the RAS included CKD, diabetes, decompensated

congestive heart failure, volume depletion, advanced age, and use of concomitant medications that interfere with kidney potassium excretion.[67] Patients with these risk factors, however, are also the same population who would be expected to derive the greatest cardiovascular and kidney benefits from these drugs. Although there are no RCTs testing the benefits and harms of mitigating hyperkalemia in order to continue RAS blockade therapy, stopping RAS blockers or reducing the RAS blocker dose has been associated with increased risk of cardiovascular events in observational studies.[68, 69]

Therefore, identifying patients at risk of hyperkalemia and instituting preventive measures should allow these patients to benefit from RAS blockade.

Measures to control high potassium levels include the following[70]:

- Moderate potassium intake, with specific counseling to avoid potassium-containing salt substitute[71] or food products containing the salt substitute.
- Review the patient's current medication and avoid drugs that can impair kidney excretion of potassium. History of the use of over-the-counter nonsteroidal anti-inflammatory drugs, supplements, and herbal treatments should be pursued, and patients should be counseled to discontinue these remedies if present.
- General measures to avoid constipation should include enough fluid intake and exercise.
- Initiate diuretics treatment to enhance the excretion of potassium in the kidneys.[65, 72-77] Diuretics can precipitate acute kidney injury (AKI) and electrolyte abnormalities, and the hypokalemic response to diuretics is diminished with low eGFR and depends on the type of diuretic used. Diuretics are most compelling for hyperkalemia management when there is concomitant volume overload or hypertension.
- Treatment with oral sodium bicarbonate is an effective strategy in minimizing the risk of hyperkalemia in patients with CKD and metabolic acidosis.[78] Concurrent use with diuretics will reduce the risk of fluid overload that could be a concern from sodium bicarbonate treatment.
- Treatment with gastrointestinal cation exchangers, such as patiromer or sodium zirconium cyclosilicate, where each has been used to treat hyperkalemia associated with RAS blockade therapy for up to 12 months.[79, 80] Such treatment may be considered when the above measures fail to control serum potassium levels. Both studies demonstrated the effectiveness of achieving normokalemia and that treatment with RAS blockade agents can be continued without treatment-related serious adverse effects. However, clinical outcomes were not evaluated; efficacy and safety data beyond 1 year of treatment are not available; and cost and inaccessibility to the drugs in some countries remain barriers to their utilization.

For the various interventions to control high potassium, pre-existing polypharmacy, costs, and patient preferences should be considered when choosing among the options.

Practice Point 1.2.6: Reduce the dose or discontinue ACEi or ARB therapy in the setting of either symptomatic hypotension or uncontrolled hyperkalemia despite the medical treatment outlined in Practice Point 1.2.5, or to reduce uremic symptoms while treating kidney failure (eGFR <15 ml/min per 1.73 m^2).

The dose of an ACEi or ARB should be reduced or discontinued only as a last resort in patients with hyperkalemia after the measures outlined above have failed to achieve a normal serum potassium level. Similar efforts should be made to discontinue other concurrent blood pressure medication before attempting to reduce the ACEi or ARB dose in patients who experience symptomatic hypotension.

When these drugs are used in patients with eGFR <30 ml/min per 1.73 m^2, close monitoring of serum potassium level is required. Withholding these drugs solely on the basis of the level of kidney function will unnecessarily deprive many patients of the cardiovascular benefits they otherwise would receive, particularly when measures could be undertaken to mitigate the risk of hyperkalemia. However, in patients with advanced CKD who are experiencing uremic symptoms or dangerously high serum potassium levels, it is reasonable to discontinue ACEi and ARB treatment temporarily with the aim of resolving any hemodynamic reductions in eGFR and reducing symptoms to allow time for kidney replacement therapy preparation.

Practice Point 1.2.7: Use only one agent at a time to block the RAS. The combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.

Combination therapy with ACEi, ARBs, or direct renin inhibitors reduces blood pressure and albuminuria to a larger extent than does monotherapy with these agents. Long-term outcome trials in patients with diabetes and CKD demonstrated no kidney or cardiovascular benefit of RAS blockade with combined therapy to block the RAS versus the single use of RAS inhibitors. However, combination therapy was associated with a higher rate of hyperkalemia and AKI,[81, 82] and thus only one agent at a time should be used to block the RAS.

1.3 Sodium–glucose cotransporter-2 inhibitors (SGLT2i)

Patients with T2D and CKD are at increased risk of both cardiovascular events and progression to kidney failure. Thus, preventive treatment strategies that reduce both the risk of adverse kidney and cardiovascular outcomes are paramount. There is substantial evidence confirming that SGLT2i confer significant kidney and heart protective effects in these patients. This was demonstrated in:

(i) Three large RCTs reporting on efficacy for primary cardiovascular outcomes and secondary kidney outcomes: the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose [EMPA-REG] trial, CANagliflozin cardioVascular Assessment Study [CANVAS], and Dapagliflozin Effect on CardiovascuLAR Events [DECLARE-TIMI 58] trial)[83-86]. Subsequently, there was an additional RCT of patients with T2D and ASCVD which found non-inferiority for cardiovascular outcomes with an SGLT2i, including among CKD subgroups (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV))[87]

(ii) A meta-analysis of 3 cardiovascular outcome trials (EMPA-REG, CANVAS, DECLARE-TIMI 58) which was stratified by CKD subgroups[88]; this analysis was before VERTIS CV was published.

(iii) Two RCTs which specifically enrolled a CKD population and was designed to evaluate primary kidney outcomes but also reporting on secondary cardiovascular outcomes; (Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) [89] and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD))[90]

(iv) A primary cardiovascular outcome RCT that exclusively enrolled patients with diabetes and CKD (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED))[91]

(v) A meta-analysis of 4 trials (EMPA-REG, CANVAS, CREDENCE, DECLARE-TIMI 58) evaluating kidney outcomes[92]; another later meta-analysis evaluating cardiovascular and kidney outcomes that also included VERTIS CV for 5 total trials;[93] and another meta-

analysis[94] of cardiovascular outcomes among the 3 trials that enrolled an exclusive CKD population (CREDENCE, DAPA-CKD, and SCORED).

(vi) Four RCTs that enrolled patients with heart failure evaluating primary cardiovascular outcomes, but also reported on secondary kidney outcomes. Two of these trials enrolled patients with heart failure and reduced ejection fraction (HFrEF) among adults with and without T2D (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF)[95] and Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced),[96] These trials also stratified by eGFR (<60 and ≥60 ml/min per 1.73 m^2) (Figure 5).One trial enrolled patients with heart failure and preserved ejection fraction (HFpEF) with and without T2D (The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved)).[97] Another trial enrolled patients with diabetes with recent acute hospitalized heart failure with or without reduced ejection fraction (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF)).[98]

SGLT2i lower blood glucose levels by inhibiting kidney tubular reabsorption of glucose. They also have a diuretic effect, as the induced glycosuria leads to osmotic diuresis and increased urine output. SGLT2i also appear to alter fuel metabolism, shifting away from carbohydrate utilization to ketogenesis. In a prior meta-analysis of 45 RCTs, SGLT2i conferred modest lowering of HbA1c (mean difference 0.7%), lowering of systolic blood pressure (4.5 mm Hg), and weight loss (–1.8 kg).[99] However, despite these relatively modest, albeit favorable, improvements in cardiovascular risk factors, SGLT2i demonstrated substantial reductions in both composite cardiovascular outcomes and composite kidney outcomes. The cardiovascular and kidney benefits appear independent of glucose-lowering, suggesting other mechanisms for organ protection, such as reduction in intraglomerular pressure and single-nephron hyperfiltration leading to preservation of kidney function.[100]

The DAPA-CKD[90] and SCORED[91] trials enrolled CKD patients with an eGFR down to as low as 25 ml/min per 1.73 m^2. The EMPEROR-Reduced[96] and EMPEROR-Preserved[97] trials, although not an exclusive CKD population, did allow enrollment patients with an eGFR as low as 20 ml/min per 1.73 m^2. There has been no evidence of effect modification for the effect of the drug based on the population (i.e., with/without heart failure and by GFR levels).

Currently, the safety and efficacy of SGLT2i for people with an eGFR <20 ml/min per 1.73 m^2, in kidney transplant recipients, or among individuals with T1D, are not established and are currently being studied; further studies will help clarify the kidney and cardiovascular benefits among these subgroups.

Figure 5. Cardiovascular and kidney outcome trials for SGLT2 inhibitors

	CREDENCE	DAPA-CKD	EMPA-REG	CANVAS	DECLARE-TIMI 58
Drug	Canagliflozin 100 mg once daily	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg, 25 mg once daily	Canagliflozin 100 mg, 300 mg once daily	Dapagliflozin 10 mg once daily
Total of participants	4401	4304	7020	10,142	17,160
% with CVD	50	37.4	100	66	41
eGFR criteria for enrollment (ml/min per 1.73 m²)	30–90	25–75	≥30	≥30	CrCl ≥60 ml/min, 45% had eGFR 60–90
Mean eGFR at enrollment (ml/min per 1.73 m²)	56	43	74	76	85
% with eGFR <60	59	88	26	20	7.4
ACR	Criteria: ACR >300–5000 mg/g [30–500 mg/mmol] Median ACR 927 mg/g [92.7 mg/mmol]	ACR 200–5000 mg/g [20–500 mg/mmol] ACR Median DAPA: 965 mg/g [96.5 mg/mmol]; Placebo: 934 mg/g [93.4 mg/mmol]	No criteria ACR <30 mg/g [3 mg/mmol] in 60%; 30–300 mg/g [3–30 mg/mmol] in 30%; >300 mg/g [30 mg/mmol] in 10%	No criteria Median ACR 12.3 mg/g [1.23 mg/mmol]	No criteria
Follow-up (yr)	2.6	2.4	3.1	2.4	4.2
Primary outcome(s)	Composite kidney	First occurrence of a ≥50% decline in eGFR, the onset of kidney failure, or death from renal or CV causes	MACE	MACE	1) MACE; 2) Composite CV death or hospitalization for HF
CV outcome results	CV death, MI, stroke: HR: 0.80; 95% CI: 0.67–0.95; hospitalization for HF: HR: 0.61; 95% CI: 0.47–0.80	CV death: HR: 0.81; 95% CI: 0.59–1.21	MACE: HR: 0.86; 95% CI: 0.74–0.99; hospitalization for HF: HR 0.65; 95% CI 0.50–0.85	MACE: HR: 0.86; 95% CI: 0.75–0.97; hospitalization for HF: HR 0.67; 95% CI: 0.52–0.87	MACE: HF: 0.93; 95% CI: 0.84–1.03; CV death or hospitalization for HF: HR 0.83; 95% CI: 0.73–0.95
Kidney outcome	Composite of kidney failure outcomes, doubling SCr, or death from renal or CV causes	First occurrence of a ≥50% decline in eGFR, the onset of kidney failure, or death from renal or CV causes	Incident or worsening nephropathy (progression to severely increased albuminuria, doubling of SCr, initiation of KRT, or renal death) and incident albuminuria	Composite doubling in SCr, kidney failure, or death from renal causes	Composite of ≥40% decrease in eGFR to <60 ml/min per 1.73 m², kidney failure, CV or renal death
Kidney outcome results	Primary kidney: HR: 0.70; 95% CI: 0.59–0.82	Primary outcome: HR: 0.61; 95% CI: 0.45–0.73	Incident/worsening nephropathy: 12.7% vs. 18.8% in empagliflozin vs. placebo. [HR: 0.61; 95% CI: 0.53–0.70] Incident albuminuria: NS	Composite kidney: 1.5 vs. 2.8 1000 patient-years in the canagliflozin vs. placebo [HR: 0.53; 95% CI: 0.33–0.84]	Composite kidney: HR: 0.76; 95% CI: 0.67–0.87

	SCORED	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	SOLOIST-WHF	VERTIS-CV
Drug	Sotagliflozin 200 mg, 400 mg once daily	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg once daily	Empagliflozin 10 mg once daily	Sotagliflozin 200 mg, 400 mg once daily	Ertugliflozin 5mg, 15 mg once daily
Total of participants	10,584	4744	3730	5988	1222	8246
% with CVD	100	100	100	100	100	100
eGFR criteria for enrollment	25–60 ml/min per 1.73 m^2	≥30 ml/min per 1.73 m^2	>20 ml/min per 1.73 m^2	No criteria	No criteria	No criteria
Mean eGFR at enrollment (ml/min per 1.73 m^2)	44	66	62	61	50	76
% with eGFR <60	100	100	88.2	49.9	69.9	21.9
ACR	No criteria ACR <30 mg/g [3 mg/mmol] in 35%; ACR 30–<300 mg/g [3–30 mg/mmol] in 34%; ACR ≥300 mg/g [≥30 mg/mmol] in 31%	No criteria	No criteria	No criteria	No criteria	No criteria
Follow-up (yr)	1.3	1.5	1.3	2.2	0.76	3.5
Primary outcome(s)	Deaths from CV causes, hospitalizations for HF, and urgent visits for HF	CV death or worsening HF	CV death or hospitalization for HF	CV death or hospitalization for HF	Deaths from CV causes and hospitalizations and urgent visits for HF	MACE
CV outcome results	Primary outcome: HR: 0.74; 95% CI: 0.63–0.88	Primary outcome: HR: 0.74; 95% CI: 0.65–0.85	Primary outcome: HR: 0.75; 95% CI: 0.65–0.86	Primary outcome: HR: 0.79; 95% CI: 0.69–0.90	Primary outcome: HR: 0.67; 95% CI: 0.52, 0.85	MACE: HR: 0.97; 95% CI: 0.85–1.11
Kidney outcome	First occurrence of a sustained decrease in GFR ≥50% for ≥30 days, long-term dialysis, kidney transplantation, or a sustained eGFR <15 ml/min per 1.73 m^2 for ≥30 days	Composite of worsening kidney function (sustained decline of eGFR ≥50%, kidney failure, or renal death)	Chronic dialysis or kidney transplant or ≥40% sustained reduction in eGFR or sustained eGFR <15 ml/min per 1.73 m^2 in patients with a baseline eGFR ≥30 ml/min per 1.73 m^2 or sustained eGFR of <10 ml/min per 1.73 m^2 in patients with a baseline GFR of <30 ml/min per 1.73 m^2	Composite kidney outcome	Not reported	Composite of kidney death, kidney replacement therapy, or doubling of SCr
Kidney outcome results	Composite kidney outcome: HR: 0.71; 95% CI 0.46–1.08	Composite kidney outcome: HR: 0.71; 95% CI: 0.44–1.16	Composite kidney outcome: HR: 0.50; 95% CI: 0.32–0.77	Composite kidney outcome: HR: 0.95; 95% CI: 0.73–1.24	N/A	Composite kidney outcome: HR: 0.81; 95% CI: 0.63–1.04

ACR, albumin-creatinine ratio; CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate;

ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; KRT, kidney replacement therapy; MACE, major adverse cardiovascular events; MI, myocardial infarction; NS, not significant; SCr, serum creatinine; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes

Recommendation 1.3.1: We recommend treating patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i (1A).

This recommendation places a high value on the kidney and heart protective effects of using an SGLT2i in patients with T2D and CKD, and a lower value on the costs and adverse effects of this class of drug. The recommendation is strong because in the judgment of the Work Group, all or nearly all well-informed patients would choose to receive treatment with an SGLT2i.

Key information

Balance of benefits and harms

Details for cardiovascular, heart failure, and kidney outcomes are summarized below.

Cardiovascular outcomes

The EMPA-REG trial enrolled over 7000 patients with T2D, baseline glycated hemoglobin (HbA1c) of 7%–10%, established CVD (almost 100%), and an eGFR of at least 30 ml/min per 1.73 m^2.[96] Of these, 1819 (25.9%) participants had an eGFR <60 ml/min per 1.73 m^2. Participants were randomized to 10 or 25 mg of empagliflozin versus placebo and followed for a median of 3.1 years. In the overall trial, empagliflozin reduced 3-point major adverse cardiovascular events (MACE) by 14% (HR: 0.86; 95% CI: 0.74–0.99).

Among participants in EMPA-REG with an eGFR of 30–60 ml/min per 1.73 m^2, there was a trend for benefit for the primary cardiovascular outcome that was not statistically significant in this subgroup, but there was no evidence for heterogeneity of treatment effect across all eGFR subgroups (*P*-interaction = 0.20). In a prespecified analysis from EMPA-REG of patients with prevalent kidney disease defined as an eGFR <60 ml/min per 1.73 m^2 and/or an ACR >300 mg/g, empagliflozin compared to placebo was associated with reduction in cardiovascular death (HR: 0.71; 95% CI: 0.52–0.98), all-cause mortality (HR: 0.76; 95% CI: 0.59–0.99), and heart failure hospitalization (HR: 0.61; 95% CI: 0.42–0.87).[101]

The CANVAS program, which combined data from 2 RCTs (CANVAS and CANVAS-R) enrolled over 10,000 patients with T2D, HbA1c between 7.0% and 10.5%, and an eGFR of at least 30 ml/min per 1.73 m^2.[83] Approximately two-thirds (66%) of participants had established CVD, and 2039 (20.1%) had CKD with an eGFR <60 ml/min per 1.73 m^2. Participants were randomized to canagliflozin 100 or 300 mg per day versus placebo and followed for a median of 2.4 years. Like EMPA-REG, the SGLT2i canagliflozin also reduced MACE by 14% (HR: 0.86; 95% CI: 0.75–0.97).

In subgroup analyses from the CANVAS trial, those with an eGFR of 30–60 ml/min per 1.73 m^2 also experienced cardiovascular benefit for the primary MACE outcome (HR: 0.70; 95% CI: 0.55–0.90), with no evidence of heterogeneity of treatment effect by eGFR status (*P*-interaction = 0.20).

The DECLARE-TIMI 58 trial enrolled 17,160 participants with an HbA1c level of 6.5%–12%. Only 41% had established CVD; the other 59% had multiple cardiovascular risk factors, so it was largely a primary prevention trial.[85] Although creatinine clearance of ≥60 ml/min was an eligibility criterion, there were 1265 participants (7.4%) who had an eGFR <60 ml/min per 1.73 m^2. Participants were randomized to dapagliflozin 10 mg per day versus placebo and followed for a median of 4.2 years. In

the main trial, dapagliflozin met its primary safety endpoint of noninferiority for MACE, but superiority for MACE (1 of 2 primary endpoints) did not reach statistical significance. However, dapagliflozin did reduce the second primary efficacy outcome of cardiovascular death or hospitalization for heart failure (HR: 0.83; 95% CI: 0.73–0.95).[85] There was also no evidence of heterogeneity by eGFR subgroups of primary efficacy outcomes of cardiovascular death or heart failure hospitalization (*P*-interaction = 0.37) or MACE outcome by eGFR subgroups (*P*-interaction = 0.99).

The VERTIS CV trial enrolled 8246 patients with T2D and ASCVD (22% of participants had eGFR <60 ml/min per 1.73 m^2) and demonstrated non-inferiority of ertugliflozin versus placebo for the primary outcome of 3-point MACE.[87] While there was a trend for benefit for the key secondary endpoint of cardiovascular death or heart failure hospitalization, this did not meet statistical significance (HR: 0.88; (95% CI: 0.75–1.03). There was no significant interaction for either the primary or secondary cardiovascular outcomes when stratified by CKD subgroups.

In the CREDENCE trial among patients with T2D with CKD (discussed further below for primary kidney outcome), canagliflozin reduced the risk of the secondary cardiovascular outcomes of hospitalization for heart failure and MACE by 39% (HR: 0.61; 95% CI: 0.47–0.80) and 20% (HR: 0.80; 95% CI: 0.67–0.95), respectively.[89]

In the DAPA CKD trial which enrolled patients with CKD with and without T2D (discussed further below for primary kidney outcome), dapagliflozin reduced the risk of the secondary cardiovascular outcome of death from cardiovascular cause or hospitalization for heart failure by 29% (HR: 0.71; 95% CI: 0.55–0.92).[90]

The SCORED trial which enrolled patients with T2D and CKD was ended early due to loss of funding.[91] The primary cardiovascular endpoint was changed during the trial to a composite of cardiovascular death, heart failure hospitalizations, or urgent visits for heart failure. Sotagliflozin reduced this primary outcome by 26% (HR: 0.74; 95% CI: 0.63–0.88); of note, sotagliflozin also reduced the original coprimary endpoint of cardiovascular death and heart failure hospitalizations by 23% (HR: 0.77; 95% CI: 0.66–0.91).

The number of participants with T2D and CKD (eGFR 30 to <60 ml/min per 1.73 m^2) and the number of events were relatively small across all these trials. Thus, a 2019 meta-analysis pooled data from the EMPA-REG, CANVAS program, and DECLARE-TIMI 58 trials and examined cardiovascular outcomes among individuals with and without CKD.[88] For those trial participants with an eGFR of 30 to <60 ml/min per 1.73 m^2, an SGLT2i similarly reduced the risk of hospitalization for heart failure (HR: 0.60; 95% CI: 0.47–0.77) and MACE (HR: 0.82; 95% CI: 0.70–0.95).

Another meta-analysis examined the pooled effects of the 3 trials that enrolled an exclusively CKD population (CREDENCE, DAPA-CKD, and SCORED) and confirmed the benefit of SGLT2i for reducing the composite cardiovascular outcome of heart failure hospitalizations or cardiovascular death (HR: 0.73; 95% CI: 0.65–0.82).

Heart failure outcomes

In the original cardiovascular outcome trials with SGLT2i among patients with T2D, there was a significant reduction in the risk of hospitalizations for heart failure that was consistent across all 3 trials (EMPA-REG, CANVAS, and DECLARE-TIMI 58). This result was also confirmed in a real-world registry, with the reduction in risk of hospitalization for heart failure and cardiovascular death associated with SGLT2i, mirroring the favorable benefits seen in the RCTs.[102]. This led to dedicated trials of SGLT2i specifically among patients with heart failure.

The DAPA-HF trial enrolled 4744 patients with symptomatic HFrEF defined as ejection fraction ≤40%, with an eGFR ≥30 ml/min per 1.73 m^2 (mean eGFR 66 ml/min per 1.73 m^2), including 55% of individuals without diabetes.[95] Over a median of 18.2 months, the primary outcome of cardiovascular

death, heart failure hospitalization, or urgent heart failure visit occurred in 16.3% of the dapagliflozin group and 21.2% of the placebo group (HR: 0.74; 95% CI: 0.65–0.85). The primary outcome was similarly reduced for individuals with and without diabetes with no effect of heterogeneity by diabetes status. The primary outcome was also similar among those with an eGFR ≥60 ml/min per 1.73 m^2 (HR: 0.76; 95% CI: 0.63–0.92) or <60 ml/min per 1.73 m^2 (HR: 0.72; 95% CI: 0.59–0.86). This finding suggests a potential role for cardiovascular benefit among CKD patients with HFrEF, even without the presence of diabetes.

The EMPEROR-Reduced trial enrolled 3730 patients with HFrEF defined as ejection fraction ≤40%, with an eGFR ≥20 ml/min per 1.73 m^2 (mean eGFR 62 ml/min per 1.73 m^2), including 50% of individuals with T2D.[96] Over a median of 16 months, the primary outcome of cardiovascular death or heart failure hospitalization occurred in 19.4% of the empagliflozin group and 24.7% of the placebo group (HR: 0.75; 95% CI: 0.65–0.86). As seen in DAPA-HF, the primary outcome was similarly reduced for individuals with and without diabetes. The primary outcome among those with an eGFR ≥60 ml/min per 1.73 m^2 was HR: 0.67; 95% CI: 0.55–0.83 and for those with eGFR <60 ml/min per 1.73 m^2 was HR: 0.83; 95% CI: 0.69–1.00. A composite kidney outcome HR of 0.50 (95% CI: 0.32–0.77) was also reported.

A recent meta-analysis of both DAPA-HF and EMPEROR-Reduced trials further revealed a composite outcome on first hospitalization for heart failure or cardiovascular death of HR: 0.72 (95% CI: 0.62–0.82) for an eGFR ≥60 ml/min per 1.73 m^2 and HR: 0.77 (95% CI: 0.68–0.88) for eGFR <60 ml/min per 1.73 m^2; a composite kidney outcome HR: 0.62; 95% CI: 0.43–0.90 (P = 0.013) was also reported.[103]

The EMPEROR-Preserved trial enrolled 5988 patients, with or without T2D, with class II-IV heart failure symptoms and an ejection fraction ≥40%.[97] Empagliflozin, compared to placebo, reduced the risk of the primary outcome of cardiovascular death or hospitalization for heart failure by 21% (HR: 0.79; 95% CI: 0.69–0.90). This benefit was again similar among patients with or without diabetes. Fifty percent of study participants had an eGFR <60 ml/min per 1.73 m^2, and there was no significant interaction by eGFR status (≥60 vs <60 ml/min per 1.73 m^2) for the primary cardiovascular outcome.

The SOLOIST trial enrolled patients with T2D who had recently been hospitalized for worsening heart failure (with or without reduced ejection fraction), of which 70% of patients had an eGFR <60 ml/min per 1.73 m^2.[98] The primary end point was deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure (first and subsequent events). The trial was stopped early, but sotagliflozin did reduce the primary outcome by 33% (HR: 0.67; 95% CI: 0.52–0.85). There was no significant interaction by eGFR status for the primary outcome.

Kidney outcomes

EMPA-REG (empagliflozin vs. placebo) also evaluated a prespecified kidney outcome of incident or worsening nephropathy, defined as progression to severely increased albuminuria (ACR >300 mg/g [30 mg/mmol]), doubling of serum creatinine, accompanied by an eGFR ≤45 ml/min per 1.73 m^2, initiation of kidney replacement therapy, or renal death. This incident or worsening nephropathy outcome was lower in the empagliflozin group—12.7% versus 18.8%—with a HR of 0.61 (95% CI: 0.53–0.70).[100]

In the CANVAS program (overall cohort including those with and without baseline CKD), canagliflozin also conferred kidney benefit, with a 27% lower risk of progression of albuminuria (HR: 0.73; 95% CI: 0.67–0.79) and a 40% (HR: 0.60; 95% CI: 0.47–0.77) lower risk of a composite kidney outcome (≥40% reduction in eGFR, need for kidney replacement therapy, or death from renal cause).[83] The CANVAS program further reported additional prespecified kidney outcomes.[84] The composite kidney outcome of doubling of serum creatinine, kidney failure, and death from renal causes occurred in 1.5 versus 2.8 per 1000 patient-years in the canagliflozin versus placebo groups (HR: 0.53; 95% CI: 0.33–0.84). There was also a reduction in albuminuria and an attenuation of eGFR decline.[84]

In the DECLARE-TIMI 58 trial (dapagliflozin vs. placebo), there was a 1.3% absolute and 24% relative risk reduction in the secondary kidney outcome (a composite of a ≥40% decrease in eGFR to <60 ml/min per 1.73 m^2, kidney failure, and cardiovascular or renal death: HR: 0.76; 95% CI: 0.67–0.87).[85] In the DAPA-HF trial, the secondary outcome of worsening kidney function (defined as a sustained ≥50% reduction in eGFR, kidney failure, or renal death) occurred in 1.2% of the dapagliflozin arm and 1.6% of the placebo arm (HR: 0.71; 95% CI: 0.44–1.16), which was not statistically significant (P = 0.17).[95, 104] However, the median duration of the DAPA-HF trial was only 18.2 months, which may not have been long enough to accumulate kidney endpoints.

The aforementioned 2019 meta-analysis pooled data from the EMPA-REG, CANVAS program, and DECLARE-TIMI 58 trials and examined kidney outcomes among individuals with and without CKD.[88] For those trial participants with an eGFR of 30 to <60 ml/min per 1.73 m^2, SGLT2i reduced the risk of adverse kidney outcomes (composite worsening kidney failure, kidney failure, or renal death; HR: 0.67; 95% CI: 0.51–0.89).

In the VERTIS CV trial, there was a trend for benefit for the secondary kidney outcome which was a composite of death from renal causes, renal replacement therapy, or doubling of the serum creatinine level, which was not statistically significant (HR: 0.81; 95% CI: 0.63–1.04).[87]

In the aforementioned cardiovascular outcome trials, kidney events were secondary outcomes and not the primary focus. Furthermore, although the above meta-analysis suggested consistent results in subgroup categories of lower kidney function, it also appeared to suggest some attenuation of kidney benefit as the eGFR worsened with the largest reductions among those with normal eGFR.[88]

This finding was further explored in the CREDENCE trial, which was the first RCT of an SGLT2i specifically powered for primary kidney outcomes among patients with exclusively albuminuric CKD.[89] The CREDENCE trial enrolled patients with T2D (with an HbA1c level of 6.5%–12.0%) and CKD, defined by an eGFR of 30–90 ml/min per 1.73 m^2 with albuminuria (ACR of 300–5000 mg/g [30–500 mg/mmol]), who were receiving standard of care including a maximum tolerated dose of an ACEi or an ARB. In the CREDENCE trial, 50% of patients had established CVD. Patients were randomized to canagliflozin 100 mg daily or placebo and followed for 2.6 years, with the trial stopping early for superiority as recommended by the Data Safety and Monitoring Committee. The primary kidney outcome was defined as a composite of kidney failure, doubling of serum creatinine, or death from renal or cardiovascular causes. The primary outcome occurred in 43.2 and 61.2 per 1000 patient-years in the canagliflozin and placebo arms, which translated to a 30% relative reduction in the primary kidney outcome by canagliflozin (HR: 0.70; 95% CI: 0.59–0.82). Even for the secondary outcome of dialysis, kidney transplant, or renal death, there was evidence for significant benefit (HR: 0.72; 95% CI: 0.54–0.97). There was no evidence of heterogeneity of treatment benefit of subgroups defined by eGFR or ACR (P-interactions were nonsignificant).

DAPA-CKD was the second SGLT2i trial with a primary kidney outcome. DAPA-CKD enrolled 4304 participants, with or without T2D, who had an eGFR 25-75 ml/min per 1.73 m^2 and an ACR of 200-5000 mg/g [20-500 mg/mmol], and evaluated a primary outcome of a sustained decline in the estimated GFR of at least 50%, kidney failure, or death from kidney or cardiovascular causes. Over a median of 2.4 years, dapagliflozin reduced the primary kidney outcome by 39% (HR: 0.61; 95% CI: 0.51–0.72). Findings were similar among patients with and without T2D.

In addition to the composite kidney outcomes, SGLT2i conferred less annual eGFR decline and a reduction in albuminuria or decreased progression to severely increased albuminuria.[84, 89, 100, 105] An updated 2019 meta-analysis pooled data from the 4 major RCTs of SGLT2i that evaluated major kidney outcomes (EMPA-REG, CANVAS, CREDENCE, and DECLARE-TIMI 58).[92] This analysis, which included nearly 39,000 participants with T2D, found that SGLT2i significantly reduced the risk of dialysis, kidney transplant, or renal death by 33% (RR: 0.67; 95% CI: 0.52–0.86). There was also

reduction in kidney failure and AKI. The benefits of SGLT2i on kidney outcomes were seen across all eGFR subgroups,[92] including those with an eGFR of 30–45 ml/min per 1.73 m^2.

In real-world registry data, after propensity matching, the initiation of SGLT2i was associated with a 51% reduced risk of composite kidney outcome of ≥50% eGFR decline or kidney failure (HR: 0.49; 95% CI: 0.35–0.67). This finding suggests that the kidney benefits seen in clinical trials are generalizable to clinical practice.[106]

It should be noted there is another on-going RCT which should be informative. The Study of the Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) (NCT03594110) is enrolling patients with or without T2D with CKD with either an eGFR ≥20 to <45 ml/min per 1.73 m² or eGFR ≥45 to <90 ml/min per 1.73 m² with ACR ≥200 mg/g [≥20 mg/mmol]. Compared to the prior CKD trials, this trial will include non-albuminuric CKD and enroll down to a lower eGFR of ≥20 ml/min per 1.73 m². The primary outcome is a combined cardio-kidney outcome defined as either kidney disease progression (kidney failure, a sustained decline in eGFR to <10 ml/min per 1.73 m², renal death, or a sustained decline of ≥40% in eGFR from randomization) or cardiovascular death.

Harms

There is an increased risk of diabetic ketoacidosis conferred by SGLT2i; however, this is generally a rare event in T2D, occurring in <1 per 1000 patient-years in a prior meta-analysis.[88] In the CREDENCE trial, this was 2.2 versus 0.2 per 1000 patient-years for canagliflozin versus placebo.[89]

In the CANVAS, but not the CANVAS-R, trial, there was a higher rate of fractures attributed to canagliflozin.[88] Of note, in the CREDENCE trial, which evaluated 100 mg/d of canagliflozin, there was no excess fracture rate.[89]

There is an increased risk of genital mycotic infections with SGLT2i treatment in both men and women that is consistent across all trials.[107] In the CREDENCE trial, which was conducted in a population of patients with exclusively T2D and CKD, this occurred in 2.27% of those in the canagliflozin arm versus 0.59% receiving placebo.[89] Most of the time, such infections can be managed with topical antifungal medications.[108] Self-care practices, such as daily bathing, may reduce risk of genital mycotic infections.

The increased risk of lower-limb amputations seen with canagliflozin in the CANVAS trial[83] was not reproduced in the CREDENCE trial,[89] even though this trial did implement special attention to foot care for prevention. This risk of amputations was also not seen with other SGLT2i (empagliflozin and dapagliflozin). Thus, it remains unclear whether the increased risk of lower-limb amputation in the CANVAS program was due to differing trial populations or protocols, or to chance. However, during the CREDENCE trial recruitment, an amendment was introduced, excluding those at risk for amputation. In the DAPA-HF trial, major hypoglycemia, lower-limb amputation, and fracture occurred infrequently and were similar between the 2 treatment groups.[95] Meta-analyses have suggested significant heterogeneity across trials, with increased risk of amputation limited to CANVAS and no increased risk associated with the SGLT2i class of medications overall.[109] Observational data have been inconclusive.[110, 111] Routine preventive foot care and adequate hydration may reduce risk of foot complications, as well as caution regarding the use of SGLT2i in patients with previous history of amputation.

In the DAPA CKD trial, which enrolled exclusively patients with CKD, the incidence of serious adverse events was similar between the dapagliflozin and placebo treated groups. No diabetic ketoacidosis or severe hypoglycemia was seen among patients without T2D.

In SCORED, which also enrolled an exclusively CKD populations, diarrhea, genital mycotic infections, volume depletion, and diabetic ketoacidosis were more common with sotagliflozin than

placebo. It should be noted that sotagliflozin is a unique agent that is both an SGLT1 and an SGLT2 inhibitor. Furthermore, sotagliflozin is not currently available for commercial use.

Quality of evidence

The overall quality of the evidence is high. This recommendation comes from high-quality data consisting of double-blinded, placebo-controlled RCTs of SGLT2i that enrolled a subset of patients with CKD glomerular filtration rate category (G)1–G3b (eGFR ≥30 ml/min per 1.73 m^2), a pooled meta-analysis of RCTs combining efficacy data for this CKD subset. There were three RCTs that enrolled exclusively patients with CKD, of which two of these trials had a primary kidney composite outcome and also reported on secondary cardiovascular outcomes. From these data, there is moderate to high quality evidence that SGLT2i treatment reduces undesirable consequences in patients with T2D and CKD, specifically cardiovascular death, hospitalization for heart failure, and progression of CKD to kidney failure. An update to the 2018 Cochrane systematic review and meta-analysis conducted by the ERT identified high quality evidence for most critical and important outcomes, except for hypoglycemia requiring third-party assistance, fractures, and HbA1c level, due to imprecision or study limitations (Supplementary Table S6[83, 85, 89, 91, 112-125]).[126]

- *Study design:* As discussed, there have now been 5 RCTs[83, 85, 86, 89, 90] and a meta-analysis of 4 of these trials[92] that have confirmed the significant benefits of SGLT2i on clinically meaningful kidney outcomes beyond just proteinuria as a surrogate marker. Of note, in the CREDENCE and DAPA-CKD trials, kidney outcomes were the primary outcome evaluated.[89, 90] Additionally, the ERT identified 25 relevant RCTs.[85, 87, 89, 91, 97, 98, 113-120, 122, 125, 127-135] in an updated Cochrane systematic review.[126]
- *Risk of bias* is low as these RCT studies demonstrated good allocation concealment, and adequate blinding, with complete accounting for most patients and outcome events. In the meta-analysis by Zelniker *et al.*,[88] the authors found that all 3 trials met the criteria for low risk of bias as assessed by the Cochrane tool for examining risk of bias in RCTs. The ERT-updated Cochrane review identified low risk of bias for most outcomes, apart from 4 outcomes (fracture, diabetic ketoacidosis, genital infection, HbA1c), which exhibited unclear blinding of outcome assessors for the majority of the included studies.
- *Consistency* is moderate to high, with consistency of kidney benefit across the trials and by baseline eGFR and albuminuria groups.[92] Additionally, the updated Cochrane review conducted by the ERT found no concerns regarding heterogeneity.[126]
- *Indirectness:* The RCT studies directly compared the effect of SGLT2i with placebo, with other potential confounding clinical variables generally being well-distributed between the treatment and control arms.
- *Precision* is good, as studies conducted included large numbers of study participants with acceptable event rates, and therefore narrow confidence intervals. The ERT-updated Cochrane review identified serious imprecision for 1 outcome, hypoglycemia requiring third-party assistance, because of a few events, well below the required optimal information size (as a rule of thumb value of 300 events, assuming modest effect sizes and baseline risks) resulting in the inability to exclude minimally important clinical difference.[136]
- *Publication bias*: All the published RCTs were registered at clinicaltrials.gov. Additionally, funnel plot assessments indicate no concerns regarding publication bias. All trials were funded by pharmaceutical industry but with transparent reporting in sponsor involvement in study design and conduct.

Values and preferences

The potential benefits from SGLT2i in terms of cardiovascular, heart failure, and kidney outcomes were judged to be critically important to patients. For example, patients with a history of heart failure or at high risk for heart failure might particularly benefit from this class of medications. Additionally, patients who prefer an oral agent over other injectable medication would also favor SGLT2i treatment. The Work Group also judged that there may be patient-specific factors that would reduce the preference for SGLT2i in specific patients, such as patients at increased risk of volume depletion, genital infections, or lower-limb amputation due to foot ulcerations. People with a history of urinary tract infections also may not prefer this class of medications.

The Work Group judged that nearly all clinically suitable and well-informed patients would choose to receive SGLT2i for the kidney and cardiovascular protective benefits, compared to other treatments or no treatment. Patients at high risk of side effects (such as those above) or those for whom cost, lack of insurance, or lack of local availability is an issue may choose an alternate medication.

Resource use and costs

Economic models have found use of SGLT2i to be a cost-effective strategy among patients with T2D based on cardiovascular benefits,[137, 138]. However, more recent analyses have shown that cost-effectiveness in the cardiovascular outcomes trials was primarily driven by reducing costs of CKD progression and kidney failure. In an analysis from the DECLARE-TIMI 58 trial, dapagliflozin treatment increased lifetime quality-adjusted life years (QALYs) and decreased costs of healthcare at a level that met United Kingdom thresholds for cost-effectiveness due to the kidney benefits (64% of QALY gain).[139] Additionally, analysis of real-world evidence together with cardiovascular outcome trial data found that SGLT2i use was cost effective in the United States, also primarily attributed to kidney benefits, even though costs for SGLT2i were much higher than in the United Kingdom, China, and Canada.[140]

Nevertheless, SGLT2i are cost-prohibitive for many patients. In the United States, obtaining reimbursement or preauthorizations from insurance companies for SGLT2i coverage places undue burden on health care professionals and patients. There are disparities in the insurance coverage for this class of medications and individuals' ability to pay at current costs. Availability of drugs also varies among countries and regions. Thus, treatment decisions must take into account each patient's preference about the magnitude of benefits and harms of treatment alternatives, drug availability in the country, and cost. Ultimately, some patients may not be able to afford these medications and should be guided in making informed decisions about alternatives for T2D and CKD management.

Considerations for implementation

The eGFR threshold for initiation of SGLT2i has changed over time as more evidence of benefit and safety accrue across a broader range of eGFR. Patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 have now been extensively studied in RCTs of SGLT2i. Participants with T2D and an eGFR as low as 30 ml/min per 1.73 m^2 were included in the EMPA-REG, CANVAS, and CREDENCE trials,[83, 86, 89] and efficacy and safety in these studies were consistent across both eGFR and albuminuria down to this threshold. The DAPA-CKD and SCORED trials enrolled CKD patients with an eGFR down to as low as 25 ml/min per 1.73 m^2.[90, 91] The EMPEROR-Reduced and EMPEROR-Preserved trials, although not exclusive CKD populations, did allow enrollment participants with an eGFR as low as 20 ml/min per 1.73 m^2.[96, 97]

There are now several lines of evidence demonstrating that initiating an SGLT2i in the eGFR range of 20-29 ml/min per 1.73 m^2 is safe and beneficial. Direct evidence is provided by the DAPA-CKD, SCORED, EMPEROR-Reduced, and EMPEROR-Preserved trials, which enrolled such participants by design. In addition, post-hoc analyses of CREDENCE and DAPA-CKD demonstrated that participants

who met eGFR eligibility at screening but subsequently had lower baseline eGFR prior to randomization (<30 ml/min per 1.73 m^2 and <25 ml/min per 1.73 m^2, respectively) experienced similar kidney benefits as those with baseline eGFR above eligibility thresholds.[141, 142] For eligibility, DAPA-CKD required albuminuria (≥200 mg/g), and the EMPEROR trials required a clinical diagnosis of heart failure; evidence for initiating an SGLT2i in the eGFR range of 20-29 ml/min per 1.73 m^2 is therefore strongest for patients with albuminuria or heart failure. However, within and across SGLT2i trials, benefits and harms of SGLT2i have been apparent across subgroups defined by eGFR, albuminuria, and the presence or absence of heart failure, and the preponderance of data suggests that SGLT2i are safe and offer kidney and cardiovascular benefits for patients with or without these specific characteristics. Therefore, we recommend treating patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i.

In subgroup analysis from the conducted trials, this finding held true for all patients, independent of age, sex, and race. Thus, this recommendation holds for patients of all ages, races, and both sexes. However, long-term follow-up and further collection of real-world data are needed to confirm the effectiveness and potential harms in specific patient populations.

Specifically, there is insufficient evidence evaluating the efficacy and safety of SGLT2i among kidney transplant patients who may be more vulnerable to infections due to their immunosuppressed states; further studies should clarify this issue. Therefore, this recommendation does not apply to kidney transplant recipients (see Practice Point 1.3.7).

A summary of SGLT2i agents with proven kidney or cardiovascular benefits, their FDA-approved doses, and dose adjustments as recommended in CKD are described in Figure 7.

Rationale

For patients with CKD with an eGFR ≥20 ml/min per 1.73 m^2, the current KDIGO guideline recommends using an SGLT2i for the purposes of kidney and cardiovascular protection, while metformin is still used for glucose control among patients with eGFR ≥30 ml/min per 1.73 m^2. The recommendation is strong due to the known cardiovascular and/or kidney protective effects in patients with T2D and CKD as shown in high-quality trials, such as EMPA-REG, CANVAS, DECLARE-TIMI 58, CREDENCE, DAPA-CKD, SCORED, DAPA-HF, SOLOIST, EMPEROR-Reduced and EMPEROR-Preserved. VERTIS CV showed cardiovascular non-inferiority, as well as safety. In the judgment of the Work Group, nearly all well-informed patients would prefer to receive this treatment over the risks of developing diabetic ketoacidosis, mycotic infections, and foot complications.

As mentioned above, the EMPA-KIDNEY trial is still ongoing. Once the full trial data are published, KDIGO will incorporate the new data into meta-analyses to provide updated summary estimates of SGLT2i benefits and risks.

The prioritization of SGLT2i therapy in high-risk patients such as those with CKD is consistent with the recommendations from other professional societies including the ACC,[143] the joint statement by the American Diabetes Association (ADA) and the European Association of the Study of Diabetes (EASD),[144, 145] and the joint guideline by the European Society of Cardiology (ESC) and EASD.[146] The ADA/EASD statement recommends that patients with T2D who have established ASCVD, CKD, or clinical heart failure be treated with an SGLT2i (or GLP-1 RA) with proven cardiovascular benefit as part of a glucose-lowering regimen independently of HbA1c, but with consideration of patient-specific factors.[147-150]

There is a lack of clarity across guidelines regarding initial therapy for patients not yet treated with a glucose-lowering drug. Most guidelines suggest initial therapy with metformin, whereas the ESC guideline recommends initial therapy with an SGLT2i for patients with high CVD risk. The current KDIGO guideline recommends using an SGLT2i for most patients with T2D, CKD, and an eGFR ≥20

ml/min per 1.73 m^2 and using metformin for patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2. Sequencing of interventions should be individualized to most pressing individual clinical needs (Section 1.1).

The 2019 ESC guideline provided a Class I recommendation to use SGLT2i for patients with T2D and ASCVD or at high/very high cardiovascular risk (which includes target organ damage such as CKD).[146] The difference between the ESC/EASD recommendation and the current KDIGO recommendation may stem from different judgments about the importance of the population studied in the landmark clinical trials. Thus, the evidence is particularly strong for the population corresponding to the CREDENCE and DAPA-CKD studies (ACR >200-300 mg/g [>20-30 mg/mmol] and eGFR >25–30 and ≤75-90 ml/min per 1.73 m^2). In contrast, the benefit seen for patients with less albumin excretion comes from cardiovascular outcome trials with secondary kidney outcomes.

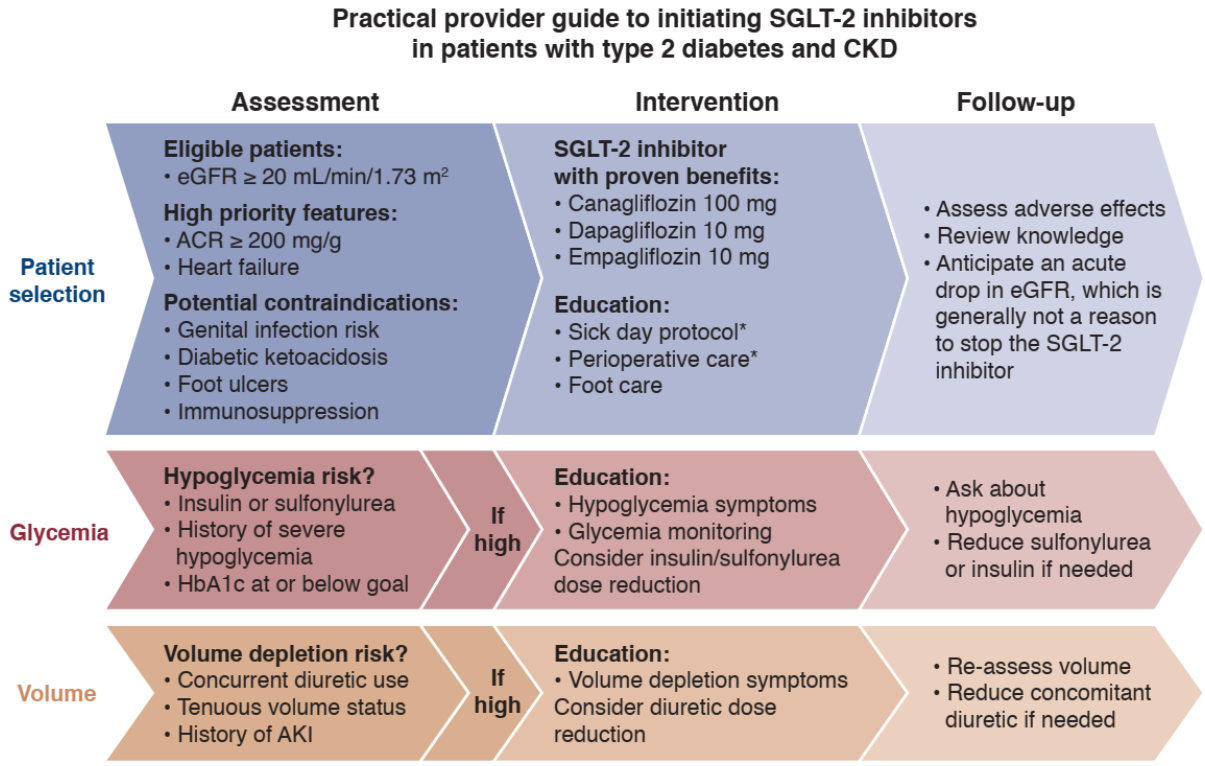
The efficacy and safety of SGLT2i has not been established in T1D. Use of SGLT2i treatment in the US remains off label, as the FDA has not approved its use in T1D. In Europe, the European Commission approved dapagliflozin and sotagliflozin for use in T1D as an adjunct to insulin in 2019. However, the drugmaker of dapagliflozin withdrew its T1D indication in 2021 citing concerns about diabetic ketoacidosis. Dapagliflozin remains approved in Japan for T1D.

Practice Point 1.3.1: The recommendation for SGLT2i is for kidney and cardiovascular protection and has been shown to have safety and benefit in CKD patients, even for those without T2D. Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to current treatment regimen (Figure 6).

For patients already being treated with glucose-lowering medications, SGLT2i can be added to existing medical regimen. The risk of hypoglycemia is low with SGLT2i monotherapy, as the drug-induced glycosuria decreases as blood glucose normalizes, but the risk may be increased when used concomitantly with other medications that can cause hypoglycemia, such as sulfonylureas or insulin.[151, 152]. These therapies may need to be adjusted if the patient's HbA1c is already below treatment target. However, notably, SGLT2i have been studied among patients without T2D who have CKD in the DAPA-CKD trial or who have heart failure (in the DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved trials) and did not confer any increased risk severe hypoglycemia or diabetic ketoacidosis among individuals without T2D.

For patients not attaining glycemic targets, see Chapter 4 on the management of hyperglycemia.

Figure 6. Practical approach to initiating SGLT2 inhibitors in patients with T2D and CKD



*Sick day protocol (for illness or excessive exercise or alcohol intake): temporarily withhold sodium-glucose cotransporter 2 inhibitor (SGLT2i), keep drinking and eating (if possible), check blood glucose and blood ketone levels more often, and seek medical help early. Periprocedural/perioperative care: inform patients about risk of diabetic ketoacidosis, withhold SGLT2i the day of day-stay procedures and limit fasting to minimum required, withhold SGLT2i at least 2 days in advance and the day of procedures/surgery requiring one or more days in hospital and/or bowel preparation (which may require increasing other glucose-lowering drugs during that time), measure both blood glucose and blood ketone levels on hospital admission (proceed with procedure/surgery if the patient is clinically well and ketones are ,1.0 mmol/L), and restart SGLT2i after procedure/surgery only when eating and drinking normally. HbA1c, hemoglobin A1c; ACR, albumin-creatinine ratio.

Practice Point 1.3.2: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Figure 7 shows current FDA-approved doses. As SGLT2i are now indicated for kidney and heart protection, independent of their glucose-lowering effect, the labels have been changed to reflect the studies that include patients with an eGFR >20-30 ml/min per 1.73 m^2.

Figure 7. SGLT2i with established kidney and cardiovascular benefits and dose adjustments as approved by the US FDA (take note of country-to-country variation)

SGLT-2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials	Dosing approved by the US FDA
Dapagliflozin	10 mg daily	eGFR ≥25 ml/min per 1.73 m^2 in DAPA-CKD eGFR ≥30 ml/min per 1.73 m^2 in DAPA-HF and DECLARE	eGFR ≥25 ml/min per 1.73 m^2
Empagliflozin	10 mg daily (Can increase to 25 mg daily if needed for glucose control)	eGFR ≥30 ml/min per 1.73 m^2 in EMPA-REG eGFR ≥20 ml/min per 1.73 m^2 in EMPEROR-Reduced and EMPEROR-Preserved	eGFR ≥30 ml/min per 1.73 m^2 for T2D and ASCVD for glucose control eGFR ≥20 ml/min per 1.73m^2 for HFrEF
Canagliflozin	100 mg daily (The higher dose of 300 mg is not recommended for CKD)	eGFR ≥30 ml/min per 1.73 m^2 in CREDENCE	eGFR ≥30 ml/min per 1.73 m^2

As DAPA-CKD and EMPA-KIDNEY allowed enrollment of patients with baseline eGFR >25 and 20 ml/min per 1.73 m^2, respectively, the eGFR level at which these SGLT2i can be initiated and maintained may be subject for revising pending future trial data. eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; SGLT2i, sodium–glucose cotransporter-2 inhibitor.

Practice Point 1.3.3: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

For patients with T2D, there is a small but increased risk of euglycemic diabetic ketoacidosis with SGLT2i (see the *Harms* section of Recommendation 1.3.1 for more details).

Practice Point 1.3.4: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

SGLT2i cause an initial natriuresis with accompanying weight reduction. This may contribute to one of the benefits of these drugs, namely, their consistent reduction in risk for heart failure hospitalizations. However, there is theoretical concern for volume depletion and AKI, particularly among patients treated concurrently with diuretics or who have tenuous volume status. Despite this theoretical concern, clinical trials have shown that the incidence of AKI is decreased with SGLT2i, compared with placebo.[92] Nonetheless, caution is prudent when initiating an SGLT2i in patients with tenuous volume status and at high risk of AKI. For such patients, reducing the dose of diuretics may be reasonable, and follow up should be arranged to monitor volume status. In older adults, adequate hydration should be encouraged.

Practice Point 1.3.5: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

The landmark RCTs demonstrated a reversible decrease in eGFR among those treated with an SGLT2i.[153] However, SGLT2i are associated with overall kidney protection with improved albuminuria, decreased progression to severely increased albuminuria, and reduction of risk from

worsening kidney impairment, kidney replacement therapy, or renal death. Pooled results of the 4 large RCTs that published results on kidney outcomes also demonstrated that risk of AKI is significantly lower with SGLT2i treatment.[92] Therefore, a modest initial drop in eGFR should not necessitate stopping the SGLT2i.

The magnitude of initial drop in eGFR that should be clinically tolerated is not well-defined. Post-hoc analyses of EMPA-REG OUTCOMES and CREDENCE suggested that a drop in eGFR ≥10% was not associated with increased risk or decreased benefits of empagliflozin and canagliflozin, respectively, compared with drop in eGFR <10%.[154, 155] In CREDENCE, a drop in eGFR ≥30% was uncommon (4% of participants assigned to canagliflozin) but was associated with modestly increased risks of kidney adverse events. Thus, one should tolerate an acute eGFR decrease of ≤30% with initiation of therapy and not discontinue therapy prematurely for an acute eGFR drop within this range. If there is a >30% decline in eGFR, ensure that the patient is not hypovolemic (e.g., adjust diuretic dose), discontinue any other nephrotoxic agents, and evaluate for alternative etiologies for kidney injury.

Practice Point 1.3.6: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.

Protocols of multiple RCTs, including CREDENCE and DAPA-CKD, specified continuation of study drug (active or placebo) even when observed eGFR dropped below the eligibility threshold specified for initiation. Since these protocols provide the evidence base for use of SGLT2i, it is prudent to follow the same approach in clinical care. Very few data are available evaluating use of SGLT2i for patients receiving dialysis, and the glucosuric actions of SGLT2i are likely insignificant with this degree of kidney failure. Therefore, it is reasonable to discontinue an SGLT2i prior to initiation of kidney replacement therapy.

Practice Point 1.3.7: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 1.3.1).

Research recommendations

- Studies focused on long-term (>5 years) safety and efficacy of SGLT2i treatment among patients with T2D and CKD. We need continued longer safety follow-up data and post-marketing surveillance.
- Studies focused on kidney and heart protective benefits of SGLT2i treatment for patients with T1D.
- Studies to establish whether there are safety and clinical benefits of SGLT2i for patients with T2D and CKD G5.
- Studies to establish whether there are safety and clinical benefits of SGLT2i for patients with T2D who are kidney transplant recipients at high risk of graft loss, CVD, and infection.
- Studies examining the safety and benefit of SGLT2i for patients with CKD and low eGFR (<30 ml/min per 1.73 m^2) without albuminuria.

- Cost-effectiveness analysis of this strategy prioritizing SGLT2i among patients with T2D and CKD, factoring in cardiovascular and kidney benefits against the cost of medications and potential for adverse effects.
- Future work to address how to better implement these treatment algorithms in clinical practice and how to improve availability and uptake among low-resource settings.
- Studies examining feasibility and barriers for developing programs to adopt novel therapies such as SGLT2i in clinical practice
- Real world studies examining outcomes of patients in health systems that incorporated SGLT2i in the management algorithm of patients with diabetes and kidney disease

1.4 Mineralocorticoid receptor antagonists (MRA)

Recommendation 1.4.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for patients with T2D, an eGFR ≥25 ml/min/1.73 m^2, normal serum potassium concentration, and albuminuria despite maximum tolerated dose of RAS inhibitor. (2A)

This recommendation places a high value on the high-quality evidence, from FIDELIO-DKD and FIGARO-DKD, that certain nonsteroidal MRA, on top of ACEi or ARB treatment, slows progressive loss of eGFR and decreases the risk of a cardiovascular event among people with T2D and albuminuria. It places a relatively lower value on the risk of hyperkalemia and monitoring of potassium during nonsteroidal MRA treatment.

Key information

Balance of benefits and harms

Clinical trials have demonstrated the kidney and cardiovascular benefits of RAS inhibitors use in those with kidney disease. Experimental evidence suggests that RAS blockade leads to incomplete suppression of serum aldosterone levels (aldosterone escape phenomenon), offering an opportunity to consider additional treatment options to lower residual albuminuria and ameliorate kidney fibrosis.[156] Steroidal MRAs, such as spironolactone and eplerenone, have established cardiovascular benefits in those with heart failure and are useful for treating primary hyperaldosteronism and refractory hypertension.[157-159] In addition, steroidal MRAs reduce albuminuria.[46] However, their effects on kidney disease progression (eGFR decline or kidney failure) have not been examined in larger trials, and hence their benefits on clinical kidney outcomes remains uncertain. Further, the use of steroidal MRA also increases the risk of hyperkalemia (by 2-3 fold) and acute kidney injury (by 2-fold), and spironolactone can cause gynecomastia.[160] These adverse effects along with the report of higher incidence of hyperkalemia after the publication of the Randomized Aldactone Evaluation Study limited the use of these agents in high-risk populations.[161]

Novel nonsteroidal MRAs, such as finerenone and esaxerenone, are more selective for mineralocorticoid receptors and noted to offer similar reductions in albuminuria but with a lower risk of

hyperkalemia.[162, 163] Recently, two large clinical trials have examined the cardiovascular and kidney effects of finerenone in those with T2D and albuminuria, enrolling patients with serum potassium levels less than 4.8 mmol/l. The FIDELIO-DKD trial included participants with (a) eGFR 25-60 ml/min per 1.73 m^2, ACR 30-<300 mg/g, and diabetic retinopathy or (b) ACR 300-5000 mg/day and eGFR 25-75 ml/min per 1.73 m^2 (Figure 8). All participants were treated with a RAS inhibitor, titrated to the maximum antihypertensive or maximum tolerated dose. There was an 18% lower incidence of primary composite outcome that included kidney failure, sustained decrease of 40% decline in eGFR, or death from renal causes with the use of finerenone.[164] While the overall frequency of adverse events between finerenone and placebo were similar, hyperkalemia-related discontinuation of study drug occurred in 2.3% among those on finerenone (vs. 0.9% in the placebo group).[165]

In the FIGARO-DKD trial, patients with ACR 30-300 mg/g and eGFR 25-90 ml/min per 1.73 m^2 or ACR 300-5000 mg/g and eGFR ≥60 ml/min per 1.73 m^2 were included (Figure 8).[166] There was a 13% lower risk of the primary cardiovascular composite outcome, which included death from cardiovascular causes, non-fatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. The secondary composite kidney outcome, which included kidney failure, sustained decrease from baseline of at least 40% in eGFR, or death from renal causes, was not significantly different between finerenone and placebo (HR 0.87, 95% CI 0.76 to 1.01). Discontinuation of trial regimen was higher among those on finerenone than placebo (1.2% vs 0.4%).

In a prespecified individual patient-level combined analysis of the FIDELIO and FIGARO trials, the cardiovascular composite was reduced in those treated with finerenone (HR: 0.86; 95% CI: 0.78-0.95). There was no significant heterogeneity in this cardiovascular benefit according to any reported baseline characteristics, including use of an SGLT2i at baseline (*P*-heterogeneity=0.41; HR: 0.63; 95% CI: 0.40-<1.00 among 877 participants using an SGLT2i) or use of a GLP-1 RA at baseline (*P*-heterogeneity=0.63; HR: 0.79; 95% CI: 0.52-1.11 among 944 participants using a GLP-1 RA). There was also a lower incidence of the kidney composite of kidney failure, >57% decrease in eGFR, or renal death among those treated with finerenone (HR: 0.77; 95% CI: 0.67-0.88), and a lower incidence of kidney failure, defined as initiation of chronic dialysis or kidney transplantation (HR: 0.80; 95% CI: 0.64-0.99).[167]

Similar to finerenone, another nonsteroidal MRA, esaxerenone lowered albumin excretion. However, the long-term kidney and cardiovascular benefits of esaxerenone have not been established.[163, 168] Hyperkalemia (potassium >6.0 or 5.5 mmol/l) occurred in 9% of the study population treated with esaxerenone.

Figure 8. Cardiovascular and kidney outcome trials for finerenone

	FIDELIO	FIGARO
Drug	Finerenone	Finerenone
Total number of participants	5734	7437
% with CVD	45.4	44.7
eGFR and ACR criteria for enrollment	25–<60 ml/min per 1.73 m^2 and ACR 30–<300 mg/g [3–<30 mg/mmol] OR 25–<75 ml/min per 1.73 m^2 and ACR 300–5000 mg/g [30–500 mg/mmol]	25–90 ml/min per 1.73 m^2 and ACR 30–<300 mg/g [3–<30 mg/mmol] OR ≥60 ml/min per 1.73 m^2 and ACR 300–5000 mg/g [30–500 mg/mmol]
Mean eGFR at enrollment (ml/min per 1.73 m^2)	44	68
% with eGFR <60 ml/min per 1.73 m^2	88.4	38.2
Median ACR at enrollment (mg/g [mg/mmol])	850 [85.0]	309 [30.9]
% with ACR ≥300 mg/g (30 mg/mmol)	87.5	50.7
Follow-up time (median, yr)	2.6	3.4
Primary outcome	Kidney composite: kidney failure, a sustained decrease ≥40% in GFR, renal death	Cardiovascular composite: death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for HF
Main secondary outcome	Cardiovascular composite: death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for HF	Kidney composite: kidney failure, a sustained decrease ≥40% in GFR, renal death
Kidney composite outcome result	HR: 0.82; 95% CI: 0.65–0.90	HR: 0.87; 95% CI: 0.76–1.01
Cardiovascular composite outcome result	HR: 0.76; 95% CI: 0.65–0.90	HR: 0.87; 95% CI: 0.76–0.98

ACR, albumin-creatinine ratio; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HF, heart failure; HR, hazard ratio; MI, myocardial infarction

Quality of evidence

The overall quality of the evidence was rated high, as nonsteroidal MRAs exhibited high quality evidence of benefit for critical composite outcomes of 4-point MACE, the composite kidney outcome, and sustained eGFR ≥57% or doubling of serum creatinine that are key to clinical decision-making.

In RCTs that compared all MRAs with placebo/standard of care (pooled nonsteroidal and steroidal MRA; Supplementary Table S7[46, 163, 164, 166, 168-177]), the quality of the evidence was downgrade largely due to limitations evident in the steroidal MRA trials. In RCTs that compared steroidal MRAs with placebo/standard of care, the quality of the evidence was rated low or very low for most of the critical outcomes, downgraded due to study limitations and serious imprecision. The quality of the evidence was rated moderate for hyperkalemia (Supplementary Tables S8[46, 163, 168-172, 174-177]).

RCTs comparing nonsteroidal MRAs with placebo/standard of care did not report peripheral vascular disease, attaining HbA1c target, and eGFR. The rationale for the quality of the evidence for each outcome is detailed below and in Supplementary Table S9[163, 164, 166, 168-170, 173, 177].

- *Study design:* Overall, the updated evidence review identified 27 RCTs on MRAs were identified, with 5 RCTs comparing nonsteroidal MRAs to placebo and/or standard of care.[164, 166, 168, 169, 177] FIDELIO-DKD was a large kidney outcomes-based trial, and FIGARO-DKD was cardiovascular outcomes-based trials respectively.[164, 166]
- *Risk of bias* for nonsteroidal MRAs is low. FIDELIO-DKD and FIGARO-DKD were well-conducted studies with no risk of bias concerns with appropriate allocation concealment, blinding, and accounting for participants and outcome events. In outcomes that only included the smaller trials,[168, 169, 177] methodological limitations due to uncertainty in reporting of allocation concealment were evident.
- *Consistency*: The updated Cochrane review found only a concern about heterogeneity for the hyperkalemia (defined K+ ≥6 mmol/l) with I^2=70%. Although, the direction of the effect is consistent, and the outcome was only downgraded by one level (serious inconsistency).
- *Indirectness:* The RCTs directly compared the effect of nonsteroidal MRAs. with placebo, with other potential confounding clinical variables generally being well-distributed between the treatment and control arms.
- *Precision:* For the critical outcomes of 4-point MACE, composite kidney outcome, and sustained eGFR decrease ≥57% or doubling serum creatinine exhibited good precision. The outcomes all-cause mortality, kidney failure, and components of 4-point MACE (stroke, myocardial infarction) did indicate benefit but did not exclude the minimally clinical important difference and hence were downgraded one level due to serious imprecision. FIDELITY undertook an individual patient data meta-analysis and found that kidney failure did not exhibit the same imprecision as demonstrated in the updated Cochrane review undertaken by the ERT.[167]
- *Publication bias*: All the published RCTs were registered at clinicaltrials.gov. Pharmaceutical industry funded by all trials. Transparent reporting and appropriate study conducted were evident in the included trials. Hence there was no evidence of undue influence of industry involvement in the reporting, conduct and analyses of the trials.

Values and preferences

The Work Group judged that the majority of well-informed patients with T2D who had persistent albuminuria and normal serum potassium despite maximal tolerated dose of RAS inhibition, and usually also an SGLT2i, would choose to receive a nonsteroidal MRA with proven kidney and heart protective benefit to further reduce risks of adverse kidney and cardiovascular outcomes. Patients with severely increased albuminuria (ACR ≥300 mg/g), who are at high risk of eGFR loss and were best represented in the FIDELIO-DKD and FIGARO-DKD trials, might be particularly inclined to choose a nonsteroidal MRA. In contrast, patients will be less inclined to choose these agents if they have lower levels of albuminuria (ACR 30-299 mg/g); uncontrolled or highly variable serum potassium or a history of hyperkalemia; or access of cost barriers to treatment with nonsteroidal MRAs.

Resource use and costs

At the time of writing, nonsteroidal MRAs are not yet available in many countries and are in the process of seeking registration with regulatory bodies. Consequently, the cost of these drugs has yet to be determined, but it is very likely that as novel therapeutic agents, they will be priced significantly higher than generic medications. The costs of nonsteroidal MRAs may be prohibitive, and therefore

may have a lower priority in the clinical treatment algorithm in low resource settings, where efforts will be made to optimize the use of less expensive drugs. In addition, the risk of hyperkalemia and monitoring of potassium during treatment may lead to higher healthcare costs due to more frequent patient visits and laboratory measurement.

Considerations for implementation

Nonsteroidal MRAs have been most rigorously tested in patients with CKD and T2D with residual cardiorenal risk, as evidenced by albuminuria (≥30 mg/g) despite treatment with standard of care, including maximal tolerated RAS blockade, and are therefore recommended for this population. So far, only finerenone has demonstrated clinical cardiovascular and kidney benefits. Nonsteroidal MRAs can cause hyperkalemia, and treatment dose and monitoring should be in accordance with the clinical trials, as described in Practice Points 1.4.3. Treatment should not be initiated if serum potassium is elevated (4.8 mmol/l was threshold at screening in the finerenone trials but per FDA label serum potassium should not be >5 mmol/l). Most incidents of hyperkalemia can be managed with treatment pauses of 72 hours, as the drug has a short half-life, and if needed general procedures to manage potassium can be applied as described in Practice Point 1.4.3.

On average, there was only a small reduction in systolic blood pressure (3 mm Hg) with finerenone compared to placebo, and no effect on HbA1c, no increase in hypo- or hyperglycemia, and no sexual side effects due to the specificity for the MRA.[164, 166] Beneficial effects of finerenone were similar (no significant heterogeneity) among participants who were also treated with SGLT2i or GLP-1 RA at baseline, and there is potentially a lower risk of hyperkalemia when finerenone was combined with an SGLT2i.[167] This suggest agents could be combined, but randomized studies have not tested if the benefits of these different agents are additive. Steroidal and nonsteroidal MRAs should not be combined due to risk of hyperkalemia.

There is no experience with pregnancy so women who are planning for pregnancy or who become pregnant on treatment should have the drug discontinued.

Rationale

MRA added to current standard of care, including ACEi or ARB treatment, has been proven to be an effective strategy to reduce albuminuria in patients with diabetes and CKD. The steroidal MRAs, spironolactone and eplerenone, have been shown to effectively reduce albuminuria, but data demonstrating that these MRAs reduce the risk of clinical outcomes are not available. The more recently-developed nonsteroidal MRAs, finerenone and esaxerenone, also reduce albuminuria, and finerenone reduced the risk of kidney and cardiovascular outcomes in two pivotal outcome trials.

Practice Point 1.4.1: Nonsteroidal MRAs are most appropriate for patients with T2D who are at high risks of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard of care therapies.

The FIDELIO-DKD and FIGARO-DKD trials enrolled people with T2D and CKD who were treated with standard of care at the time the trials were initiated, including a RAS inhibitor and appropriate medications to control glycemia and blood pressure.[164, 166] Importantly, eligibility required that participants have albuminuria (ACR ≥30 mg/g) despite these standard interventions. Patients with T2D and albuminuria are known to be at high risk of CKD progression and cardiovascular events, and the FIDELIO-DKD and FIGARO-DKD trials demonstrated that finerenone reduced these events (particularly CKD progression and heart failure) among such patients. Therefore, the most logical application of finerenone is to patients with high residual risks of CKD progression and cardiovascular

events, as evidenced by albuminuria (ACR ≥30 mg/g) despite lifestyle modifications and first-line drug therapies.

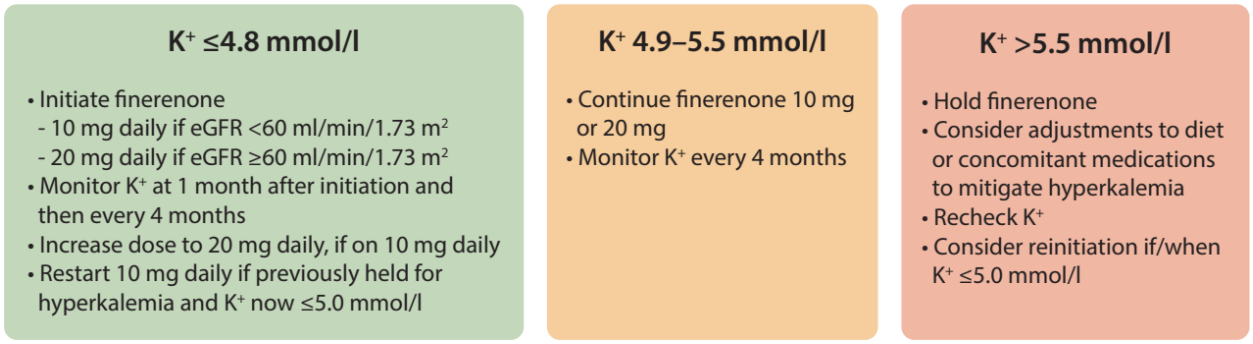
Practice Point 1.4.2. In general, SGLT2i should be initiated prior to adding a nonsteroidal MRA for treatment of T2D and CKD.

In both FIDELIO-DKD and FIGARO-DKD, a RASi was titrated to the maximum antihypertensive or maximum tolerated dose prior to randomization, consistent with the standard of care for people with T2D, albuminuria, and hypertension. Thus, clinical benefits of finerenone have only been demonstrated when added to a RASi. SGLT2i were not standard of care when the FIDELIO-DKD and FIGARO-DKD trials were initiated. However, 877 participants were using an SGLT2i at baseline, and the cardiovascular effects of finerenone, compared with placebo, appeared to be at least as beneficial among people using versus not using an SGLT2i.[167] These data, combined with complementary mechanisms of action, suggest that the benefits of SGLT2i and finerenone may be additive. This guideline issues a strong recommendation for use of an SGLT2i in the treatment of people with T2D and CKD, positioning SGLT2i as first-line drug therapy to prevent CKD progression and cardiovascular events regardless of glycemia (Figure 1 and 2). This recommendation is based on numerous clinical trials that now provide strong evidence of efficacy and safety (see *Balance of benefits and harms* section of Recommendation 1.3.1). Therefore, for patients with T2D and CKD, both a RASi and an SGLT2i should generally be prescribed prior to initiating a nonsteroidal MRA. Patients who continue to meet criteria for finerenone (including residual albuminuria and normal serum potassium on first-line therapies) can then be considered for addition of finerenone (Figure 2). In addition, finerenone may be added to a RASi alone for patients who do not tolerate or are not candidates for an SGLT2i.[165]

Practice Point 1.4.3. To mitigate risk of hyperkalemia, select patients with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA.

MRAs are known to increase serum potassium concentration and risk of hyperkalemia. To mitigate this risk, the FIDELIO-DKD and FIGARO-DKD trials restricted eligibility to patients with normal serum potassium concentration (after maximizing RASi) and implemented a standardized potassium monitoring protocol. Together, this approach yielded acceptable rates of hyperkalemia with few attributable serious adverse events. Specifically, the FIDELIO-DKD and FIGARO-DKD trial protocols mandated a serum potassium concentration consistently ≤4.8 mmol/l during screening. While some participants had a slightly higher serum potassium of 4.9-5.0 mmol/l at randomization, selection was primarily based on concentration ≤4.8 mmol/l, and patient selection in clinical practice should focus on patients who consistently meet this target. In the FIDELIO-DKD and FIGARO-DKD trials, serum potassium was checked one month after drug initiation, four months after drug initiation, and every four months thereafter. Finerenone was continued with serum potassium ≤5.5 mmol/l. With serum potassium >5.5 mmol/l, the drug was temporarily withheld and serum potassium was rechecked within 72 hours. Use of dietary potassium restriction and concomitant medications, such as diuretics and dietary potassium binders, was allowed, and the drug was reinitiated if and when potassium returned to ≤5.0 mmol/l. Clinicians should follow a similar approach to selecting and monitoring patients for nonsteroidal MRA therapy, increasing the likelihood that the acceptable adverse event profile seen in the FIDELIO-DKD and FIGARO-DKD trials is maintained when applied to clinical practice (Figure 10).

Figure 10. Serum potassium monitoring during treatment with finerenone[*†‡]*


K+ ≤4.8 mmol/l
• Initiate finerenone
- 10 mg daily if eGFR <60 ml/min/1.73 m2
- 20 mg daily if eGFR ≥60 ml/min/1.73 m2
• Monitor K+ at 1 month after initiation and then every 4 months
• Increase dose to 20 mg daily, if on 10 mg daily
• Restart 10 mg daily if previously held for hyperkalemia and K+ now ≤5.0 mmol/l
K+ 4.9–5.5 mmol/l
• Continue finerenone 10 mg or 20 mg
• Monitor K+ every 4 months
K+ >5.5 mmol/l
• Hold finerenone
• Consider adjustments to diet or concomitant medications to mitigate hyperkalemia
• Recheck K+
• Consider reinitiation if/when K+ ≤5.0 mmol/l

*Adapted from the protocols of FIDELIO-DKD and FIGARO-DKD
†FDA has approved initiation of K^+ <5.0 mmol/l. This is guided by trial design and the FDA label and may be different in other countries
‡Serum creatinine/eGFR should be monitored concurrently with sodium potassium

Practice Point 1.4.4. The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

Currently, the only nonsteroidal MRA for which long-term clinical outcomes have been rigorously ascertained is finerenone. In the FIDELIO-DKD and FIGARO-DKD trials, finerenone was started at a dose of 20 mg daily when eGFR was ≥20 ml/min per 1.73 m^2 or at a dose of 10 mg daily when eGFR was 25-59 ml/min per 1.73 m^2, with uptitration to 20 mg daily at if serum potassium remained ≤4.8 mmol/l. Steroidal MRAs do not have documented clinical kidney or cardiovascular benefits, except when heart failure, primary hyperaldosteronism, or refractory hypertension is present.

Practice Point 1.4.5. A steroidal MRA should be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low GFR.

Steroidal MRAs are standard of care for treatment of heart failure (particularly with reduced ejection fraction) and primary hyperaldosteronism.[146, 147] Steroidal MRAs are also useful for reducing blood pressure in the setting of refractory hypertension.[145] When a steroidal MRA is already used for one of these indications, there is no evidence that switching to a nonsteroidal MRA will improve outcome, and adding a nonsteroidal MRA is likely to increase adverse effects and should not be done. When a patient is treated with neither a steroidal MRA nor a nonsteroidal MRA but has indications for both (e.g., T2D with heart failure and albuminuria on first-line therapies), the most clinically pressing indication should drive selection of MRA. Currently, a nonsteroidal MRA cannot be a replacement for steroidal MRAs for the indications of heart failure and hyperaldosteronism.

Research recommendations

- More data are needed on combining MRA with other effective classes of medications, including SGLT2i and GLP-1 RA
- Trials are needed to examine the benefits and risks of MRA in additional relevant study populations, including patients with type 2 diabetes and normal urine albumin excretion, patients with type 1 diabetes and CKD, patients who have received a kidney transplant, and patients who are treated with dialysis

- Studies are needed to assess the comparative effects of steroidal and nonsteroidal MRAs, particularly for patients for whom both classes of medication may be indicated by virtue of multiple comorbidities (e.g., CKD and heart failure).
- Real-world data on the outcomes of nonsteroidal MRA use in clinical practice are needed to verify uptake effectiveness and safety outside of the clinical trial setting.
- Health economic evaluation of the implementation of nonsteroidal MRA.

1.5 Smoking cessation

Recommendation 1.5.1: We recommend advising patients with diabetes and CKD who use tobacco to quit using tobacco products (1D).

This recommendation places a high value on the well-documented health and economic benefits of avoiding tobacco products among the general population, and the absence of a strong a priori rationale for why these data would not apply to people with diabetes and CKD. The recommendation places a lower value on the lack of direct evidence for benefit in people with diabetes and CKD specifically.

Key information

Balance of benefits and harms

Tobacco use remains a leading cause of death across the globe and is also a known risk factor for the development of CKD.[178] Recent data also highlight the relationship of secondhand smoke with kidney disease.[179] Although no RCTs have examined the impact of smoking cessation on cardiovascular risk in those with CKD, observational studies have highlighted the harmful cardiovascular effects associated with smoking.[180] More recently, electronic nicotine delivery systems, referred to as e-cigarettes, have been reported to increase the risk of lung disease and CVD.[181] Data on e-cigarettes in those with kidney disease are sparse. Thus, given the preponderance of the evidence of tobacco cessation benefits reported in the general population, health care professionals should assess the use of tobacco products and counsel patients with diabetes and CKD to quit using tobacco products.

Quality of evidence

Among people with diabetes and CKD, smoking cessation interventions have been examined in only 1 small randomized crossover trial with a total of 25 participants, 10 of whom did not have diabetes and were not included in the analysis. The timeframe for this study was short: 8 hours of controlled smoking versus 8 hours of nonsmoking (in the same subjects) on separate days. The quality of the evidence from this study for surrogate outcomes was low because of very serious imprecision (only 1 study and few participants). Critical clinical outcomes, such as death, kidney failure, and cardiovascular events were not reported, and therefore the overall quality of the evidence has been rated as very low (Supplementary Table S10[182]).

Values and preferences

The cardiovascular benefits of smoking cessation and the feasibility of making attempts to stop smoking were judged to be the most important aspects to patients. The Work Group also considered that it would be important for patients to address smoking cessation during routine clinical visits despite competing issues that have to be addressed during office visits. In the judgment of the Work Group, the well-documented clinical benefits of tobacco abstinence, and the availability of various interventions in nearly all settings, justify a strong recommendation.

Resource use and costs

Smoking cessation strategies include behavioral interventions, pharmacotherapy, and a combination thereof. Behavioral interventions include assessment of tobacco use and willingness to quit, followed by counseling during office visits. Clinicians should present available treatment options to those who use tobacco products and make recommendations based on cost, affordability, and availability. These include FDA–approved treatment options, such as nicotine replacement therapy (patch, gums, lozenges, nasal spray, and inhalers) and medications, such as bupropion and varenicline, with appropriate dose adjustments depending on the level of kidney function. In the absence of expertise in offering smoking cessation therapy, referral to trained health care providers should be considered.

Considerations for implementation

Assessment of tobacco use would help physicians identify high-risk individuals. The benefits of abstinence from tobacco products are not likely to differ based on sex and race. Physicians should consider the affordability (when using nicotine-replacement products) and access to various resources while making treatment recommendations. Overall, these recommendations are similar to the 2012 KDIGO CKD guidelines, the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on the primary prevention of CVD,[1] and the US Public Health Service's Clinical Practice Guideline for Treating Tobacco Use and Dependence, which should facilitate efforts at implementation.

Rationale

Various forms of tobacco exposure continue to contribute to excess cardiovascular and other causes of death in multiple parts of the world.[183] Population-based studies note that exposure to secondhand smoke is associated with a higher prevalence of kidney disease and the development of incident kidney disease. Although use of e-cigarettes has increased over time, their safety, especially with regard to CVD, has been questioned, and their effects on kidney disease are unknown.[184, 185] Although they are not recommended as a treatment option for those with tobacco addiction, they are being used by adults who would like to quit smoking. A prospective cohort study comparing the cardiovascular risk of current or former smokers versus never smokers in diabetic patients with CKD reported higher cardiovascular events among current or prior smokers.[186] Similar findings have also been noted in other large cohort studies wherein CKD patients who were smoking had a higher risk of cardiovascular events than did nonsmokers and former smokers. In the general population, interventions that combine pharmacotherapy and behavioral support increase smoking cessation success.[187] Although dedicated trials are lacking in those with CKD, these interventions are likely to confer similar benefits in those with diabetes and CKD.[184]

Practice Point 1.5.1: Physicians should counsel patients with diabetes and CKD to reduce secondhand smoke exposure.

Secondhand smoke exposure increases the risk of adverse cardiovascular events in the general population, and associations of such events with incidence of kidney disease have also been reported.[179] As the prevalence of smoking has decreased over time and with restrictions on using tobacco products, exposure to secondhand smoke has decreased in certain countries, although the risk persists in several other regions. Thus, while assessing the use of tobacco products, exposure to secondhand smoke should also be ascertained, and patients with significant exposure should be advised of the potential health benefits of reducing such exposure.

Research recommendations

- Further examine the safety, feasibility, and beneficial effects of various interventions (e.g., behavioral vs. pharmacotherapy) for quitting tobacco product use in clinical studies.

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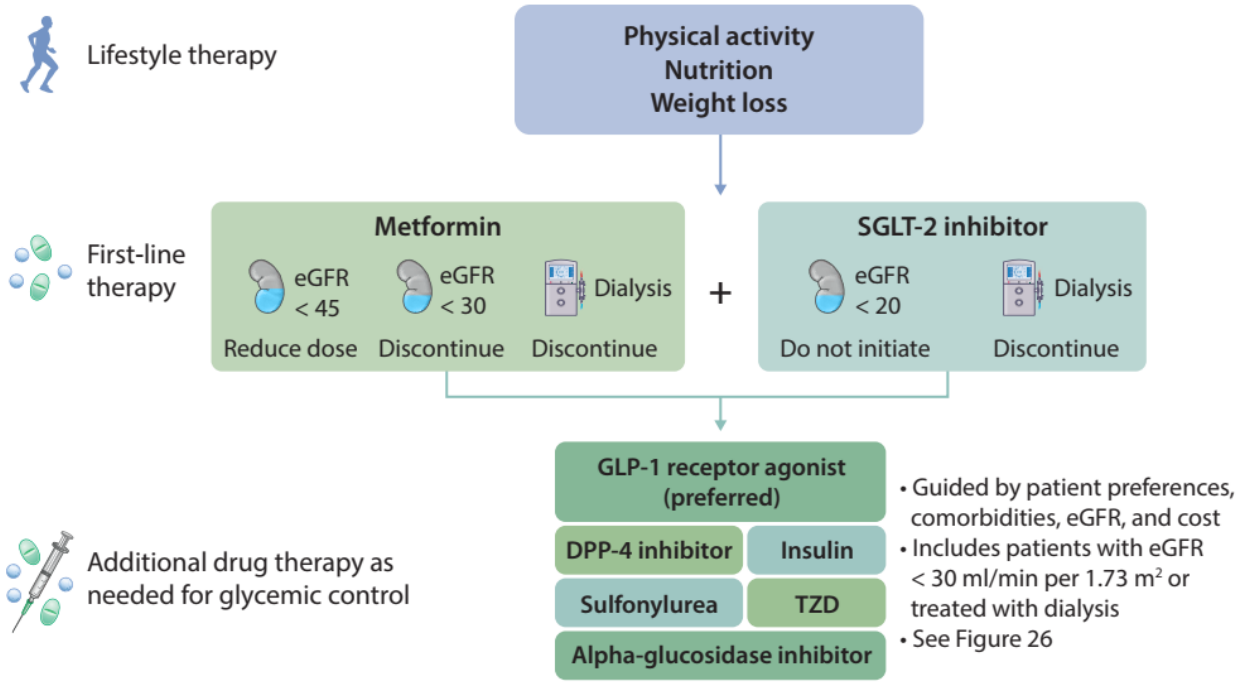
Chapter 4: Glucose-lowering therapies in patients with type 2 diabetes (T2D) and CKD

Practice Point 4.1: Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with metformin and a sodium-glucose cotransporter-2 inhibitor (SGLT2i), and additional drug therapy as needed for glycemic control (Figure 23).

Lifestyle therapy is the cornerstone of management for patients with T2D and CKD. In addition, metformin and SGLT2i should be used in combination as first-line treatment for most patients with suitable eGFR (Figure 23 and Figure 25). SGLT2i are recommended as part of comprehensive care of patients with T2D and eGFR ≥20 ml/min per 1.73 m^2 because they have been proven to reduce risks of CKD progression and major CVD events, especially heart failure (see Section 1.3). These benefits of SGLT2i do not appear to be mediated by glycemia. Nonetheless, SGLT2i do also lower blood glucose, with improvements in HbA1c that are modest and diminished at low eGFR. Similarly, metformin is an effective, safe, and inexpensive medication for first-line treatment of T2D when eGFR is ≥30 ml/min per 1.73 m^2 (see Section 4.1). Therefore, a combination of metformin and SGLT2i is a logical foundation for glycemic control in suitable patients with T2D. Additional glucose-lowering drugs can be added to this base drug therapy as needed to achieve glycemic targets. GLP-1 RA are generally preferred because they are safe and effective glucose-lowering agents with eGFR as low as 15 ml/min per 1.73 m^2, reduce risk of atherosclerotic CVD events even when eGFR is <60 ml/min per 1.73 m^2, lower albuminuria, and may slow eGFR decline. These recommendations are guided in large part by results of recent large RCTs, summarized in Figure 24 and detailed in Sections 1.3, 4.1, and 4.2.

Figure 23. Treatment algorithm for selecting glucose-lowering drugs for patients with T2D and CKD



Kidney icon indicates estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2); dialysis machine icon indicates dialysis. CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes; TZD, thiazolidinedione

Figure 24. Overview of select large, placebo-controlled clinincal outcome trials assessing the benefits and harms of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors

			Primary outcome		Kidney outcomes		
Drug	**Trial**	**Kidney-related eligibility criteria**	**Primary outcome**	**Effect on primary outcome**	**Effect on albuminuria or albuminuria-containing composite outcome**	**Effect on GFR loss***	**Adverse effects**
SGLT-2 inhibitors							
Empagliflozin	EMPA-REG OUTCOME	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA
	EMPEROR-Preserved	No criteria	CV death or hospitalization for HF	↓	NA	↔	Genital and urinary tract infections, hypotension
	EMPEROR-Reduced	eGFR >20 ml/min per 1.73 m²	CV death or hospitalization for HF	↓	NA	↓↓	Genital tract infections
Canagliflozin	CANVAS trials	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	Genital mycotic infections, DKA, amputation
	CREDENCE	ACR >300 mg/g [30 mg/mmol] and eGFR 30–90 ml/min per 1.73 m²	Progression of CKD†	↓↓	↓↓	↓↓	Genital mycotic infections, DKA
Dapagliflozin	DECLARE-TIMI 58	CrCl ≥60 ml/min	Dual primary outcomes: MACE and the composite of hospitalization for heart failure or CV death‡	↔/↓	↓	↓↓	Genital mycotic infections, DKA
	DAPA-CKD	eGFR 25–75 ml/min per 1.73 m²	First occurrence of a ≥50% decline in eGFR, the onset of kidney failure, or death from renal or CV causes	↓↓	NA	↓↓	Major hypoglycemia, volume depletion
	DAPA-HF	eGFR ≥30 ml/min per 1.73 m²	CV death or worsening HF	↓	NA	↔	None notable
Ertugliflozin	VERTIS-CV	No criteria	MACE	↔	NA	↔	Genital mycotic infection, urinary tract infections
Sotagliflozin	SCORED	eGFR 25–60 ml/min per 1.73 m²	Deaths from CV causes, hospitalizations for HF, and urgent visits for HF	↓	NA	↔	DKA, GI, genital mycotic infections, volume depletion
	SOLOIST	No criteria	Deaths from CV causes and hospitalizations and urgent visits for HF	↓↓	NA	NA	Severe hypoglycemia
GLP-1 receptor agonists							
Lixisenatide	ELIXA	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↓	↔	None notable
Liraglutide	LEADER	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↔	GI
Semaglutide§	SUSTAIN-6	Patients treated with dialysis excluded	MACE	↓	↓↓	NA	GI
	PIONEER 6	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	NA	NA	GI
Exenatide	EXSCEL	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	↔	↔	None notable
Albiglutide	HARMONY	eGFR ≥30 ml/min per 1.73 m²	MACE	↓	↔	NA	Injection site reactions
Dulaglutide	REWIND	eGFR ≥15 ml/min per 1.73 m²	MACE	↓	↓	↓	GI
Efpeglenatide	AMPLITUDE-O	eGFR 25–59.9 ml/min per 1.73 m²	MACE	↓	↓↓	↓↓	GI
DPP-4 inhibitors							
Saxagliptin	SAVOR-TIMI 53	eGFR ≥15 ml/min per 1.73 m²	MACE	↔	↓	↔	HF; any hypoglycemic event (minor and major) also more common
Alogliptin	EXAMINE	Patients treated with dialysis excluded	MACE	↔	NA	NA	None notable
Sitagliptin	TECOS	eGFR ≥30 ml/min per 1.73 m²	MACE	↔	NA	NA	None notable
Linagliptin	CARMELINA	eGFR ≥15 ml/min per 1.73 m²	Progression of CKD†	↔	↓	↔	None notable

ACR, albumin-creatinine ratio; CKD, chronic kidney disease; CrCl, creatinine clearance; CV, cardiovascular; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; GI, gastrointestinal symptoms (e.g., nausea and vomiting); GLP-1, glucagon-like peptide-1; HF, hospitalization for heart failure; MACE, major adverse cardiovascular events including myocardial infarction, stroke, and cardiovascular death (3-point MACE), with or without the addition of hospitalization for unstable angina (4-point MACE); NA, data not published; SGLT2, sodium–glucose cotransporter-2. ↔, no significant difference. ↓, significant reduction in risk, with hazard ratio (HR) estimate >0.7 and 95% confidence interval (CI) not overlapping 1. ↓↓, significant reduction in risk, with HR estimate ≤0.7 and 95% CI not overlapping 1. [*]Variable composite outcomes that include loss of eGFR, kidney failure, and related outcomes. [†]Progression of CKD defined in CREDENCE as doubling of serum creatinine, kidney failure, or death from kidney or cardiovascular causes and in CARMELINA as 40% decline in eGFR, kidney failure, or renal death. [‡]DECLARE-TIMI 58 dual primary outcomes: (i) MACE and (ii) the composite of hospitalization for heart failure or CV death. [§]SUSTAIN-6: injectable semaglutide; PIONEER 6: oral semaglutide

Practice Point 4.2: Most patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 would benefit from treatment with both metformin and an SGLT2i.

Both metformin (see Section 4.1) and SGLT2i agents (see Section 1.3) are preferred glucose-lowering medications for patients with T2D, CKD, and suitable eGFR. Metformin and SGLT2i each reduce the risk of developing diabetes complications with a low risk of hypoglycemia. Metformin has been proven to be a safe, effective, and inexpensive foundation for glycemic control in T2D with modest long-term benefits for the prevention of diabetes complications. In comparison, SGLT2i have weaker effects on HbA1c, particularly with an eGFR <60 ml/min per 1.73 m^2, but they have large effects on reducing CKD progression and CVD events, especially heart failure, that appear to be independent of eGFR.[1, 2]

In most patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2, metformin and an SGLT2i can be used safely and effectively together. In fact, the majority of the participants in the SGLT2i cardiovascular outcome trials were also treated with metformin, and many patients with T2D require more than one glucose-lowering medication to meet glycemic targets. The combination of metformin and an SGLT2i is logical because they have different mechanisms of action, and neither carries increased risk of hypoglycemia. Even when glycemic targets are achieved on metformin, an SGLT2i should be added in these patients for the beneficial effect on CKD progression and CVD risk (see Section 1.3).

For patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 not currently treated with glucose-lowering drugs (i.e., "drug naïve" patients), there are no high-quality data comparing initiation of glucose-lowering drugs therapy with metformin first versus an SGLT2i first. Given the historical role of metformin as the initial drug treatment for T2D, and the fact that most patients in cardiovascular outcome trials treated with SGLT2i were first treated with metformin, it is logical to initiate metformin first for most patients, with the anticipation that SGLT2i will be subsequently added soon after. When sequencing multiple beneficial therapies, it is critical to ensure timely follow-up and institution of step-wise plans, avoiding treatment inertia (see Chapter 1). Initial combination therapy is also a reasonable option when education and monitoring for multiple potential adverse effects are feasible. Using low doses of both an SGLT2i and metformin may be a practical approach to manage glycemia, receive the heart and kidney protection benefits of an SGLT2i (which do not appear to be dose dependent), and minimize drug exposure. For patients who have little or no need for pharmacologic agents to control glycemia, or who cannot tolerate metformin, treatment with an SGLT2i alone is reasonable in order to reduce risks of CKD progression and CVD events.

For patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 who are attaining glycemic targets with metformin as the sole glucose-lowering agent, data supporting use of an SGLT2i are limited. Specifically, all participants in the cardiovascular outcome trials for SGLT2i had an HbA1c of at least 6.5%. However, for patients attaining glycemic targets with metformin alone, addition of an SGLT2i (particularly, if both agents are used in low doses) is not likely to cause hypoglycemia and may still provide kidney and cardiovascular benefits. Kidney and cardiovascular benefits are not proven in this specific population but are supported by the observations that SGLT2i reduce kidney and cardiovascular events similarly across the full range of studied HbA1c levels (≥6.5%)[3-8] and that beneficial effects of dapagliflozin and empagliflozin on heart failure (among patients with heart failure) did not require presence of diabetes.[4, 9, 10] More data are needed to verify this approach in CKD.

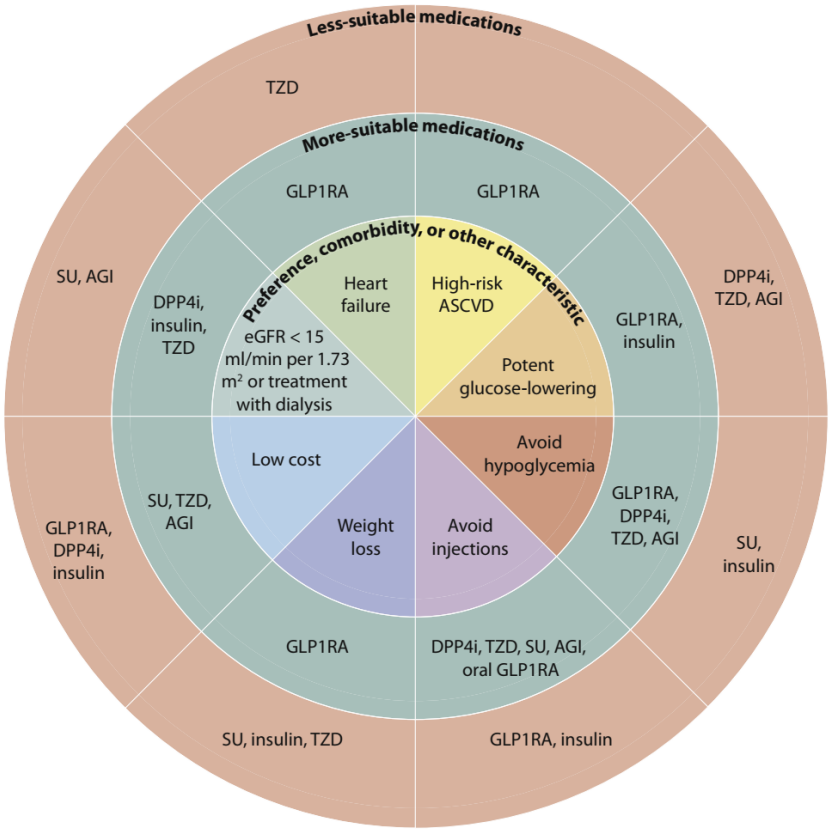
Metformin should not be initiated in patients with T2D and an eGFR <30 ml/min per 1.73 m^2, and should be discontinued when eGFR falls below 30 ml/min per 1.73 m^2, to reduce risk of lactic acidosis (Figure 23; Sections 1.3 and 4.1).[11, 12] SGLT2i can be initiated for patients with an eGFR ≥20 ml/min per 1.73 m^2, see Section 1.3). For patients whose eGFR subsequently declines below these initiation thresholds, the SGLT2i can be continued until initiation of kidney replacement therapy, in accordance

with the approach studied in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) and DAPA-CKD trials.[6, 13]

Practice Point 4.3: Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonist (GLP-1 RA) generally preferred (Figure 25).

Some patients with T2D will not achieve glycemic targets with lifestyle therapy, metformin, and SGLT2i, or they will not be able to use these interventions due to intolerances, low eGFR, or other restrictions. Glucose-lowering agents other than metformin and SGLT2i will likely be needed in these situations. GLP-1 RA are generally preferred because of their demonstrated cardiovascular benefits, particularly among patients with established ASCVD even with eGFR <60 ml/min per 1.73 m^2,[14] and benefits to reduce albuminuria and slow eGFR decline (see Section 4.3).[14, 15] Other classes of glucose-lowering agents may also be used, considering the patient factors detailed in Figure 25. DPP-4 inhibitors lower blood glucose with low risk of hypoglycemia but have not been shown to improve kidney or cardiovascular outcomes and should not be used in combination with GLP-1 RA.[16] All glucose-lowering medications should be selected and dosed according to eGFR.[17] For example, sulfonylureas that are long-acting or cleared by the kidney should be avoided at low eGFRs.[17]

Figure 25. Patient factors influencing the selection of glucose-lowering drugs other than SGLT2i and metformin in T2D and CKD



AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione

4.1 Metformin

Recommendation 4.1.1: We recommend treating patients with T2D, CKD, and an eGFR ≥30 ml/min per 1.73 m^2 with metformin (1B).

This recommendation places a high value on the efficacy of metformin in lowering HbA1c level, its widespread availability and low cost, its good safety profile, and its potential benefits in weight gain prevention and cardiovascular protection. The recommendation places a low value on the lack of evidence that metformin has any kidney protective effects or mortality benefits in the CKD population.

Key information

Balance of benefits and harms

Metformin is an effective antiglycemic agent and has been shown to be effective in reducing HbA1c in patients with T2D, with low risks for hypoglycemia in both the general population and patients with CKD. The United Kingdom Prospective Diabetes Study (UKPDS) study showed that metformin monotherapy in obese individuals achieved similar reduction in HbA1c levels and fasting plasma glucose levels, with lower risk for hypoglycemia when compared to those given sulfonylureas or insulin.[18] Moreover, a systematic review demonstrated that metformin monotherapy was comparable to thiazolidinediones (pooled mean difference in HbA1c: –0.04%; 95% CI: –0.11–0.03) and sulfonylurea (pooled mean difference in HbA1c: 0.07%; 95% CI: –0.12–0.26) in HbA1c reduction, but was more effective than DPP-4 inhibitors (pooled mean difference in HbA1c: –0.43%; 95% CI: –0.55 to –0.31).[19, 20] This result was with the added advantage of reduced risks of hypoglycemia when metformin was compared with sulfonylureas in patients with normal kidney function (odds ratio [OR]: 0.11; 95% CI: 0.06–0.20) and impaired kidney function (OR: 0.17; 95% CI: 0.11–0.26).[20]

In addition to its efficacy as an antiglycemic agent, studies have demonstrated that treatment with metformin is effective in preventing weight gain and may achieve weight reduction in obese patients. Results from the UKPDS study demonstrated that patients allocated to metformin did not show a change in mean body weight at the end of the 3-year study period, whereas body weight increased significantly with sulfonylurea and insulin treatment.[18] Similarly, this effect was reproduced in an analysis of a subgroup of patients in the UKPDS study who failed diet therapy and were subsequently randomized to metformin, sulfonylurea, or insulin therapy, with patients allocated to the metformin group having the least amount of weight gain.[21] Likewise, the same systematic review earlier showed that metformin treatment led to greater weight reduction when compared to sulfonylurea (–2.7 kg; 95% CI: –3.5 to –1.9), thiazolidinediones (–2.6 kg; 95% CI: –4.1 to –1.2) or DPP-4 inhibitors (–1.3 kg; 95% CI: –1.6 to –1.0).[19, 20]

In addition, treatment with metformin may be associated with protective effects against cardiovascular events, beyond its efficacy in controlling hyperglycemia in the general population. The UKPDS study suggested that among patients allocated to intensive blood glucose control treatment, metformin had a greater effect than sulfonylureas or insulin for reduction in diabetes-related endpoints, which included death from fatal or nonfatal myocardial infarction, angina, heart failure, and stroke.[21] An RCT performed in China, the Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus with Coronary Artery Disease (SPREAD-DIMCAD) study, looked at the effect of

metformin versus glipizide on cardiovascular events as a primary outcome. The study suggested that metformin has a potential benefit over glipizide on cardiovascular outcomes in high-risk patients, with a reduction in major cardiovascular events over a median follow-up of 5 years.[22] Indeed, in a systematic review performed, the signal for the reduction in cardiovascular mortality was again detected, with RR of 0.6–0.7 from RCTs in favor of metformin compared with sulfonylureas.[20]

Despite the potential benefits on cardiovascular mortality, the effects of metformin on all-cause mortality and other diabetic complications appeared to be less consistent in the general population. The systematic review did not demonstrate any advantage of metformin over sulfonylureas in terms of all-cause mortality or microvascular complications.[20] There was even a suggestion in the UKPDS that early addition of metformin in sulfonylurea-treated patients was associated with an increased risk of diabetes-related death of 96% (95% CI: 2%–275%, $P = 0.039$).[21]

Metformin is not metabolized and is excreted unchanged in the urine, with a half-life of about 5 hours.[23] Phenformin, which was a related biguanide, was withdrawn from the market in 1977 because of its association with lactic acidosis. Consequently, the FDA applied a boxed warning to metformin, cautioning against its use in CKD in which the drug excretion may be impaired, thereby increasing the risk of lactic acid accumulation.[24] However, the association between metformin and lactic acidosis had been inconsistent, with literature reviews even refuting this concern,[25] including in patients with an eGFR of 30–60 ml/min per 1.73 m^2.[26] Consequently, the FDA revised its warning regarding metformin use in patients with CKD, switching from a creatinine-based restriction to include eligible patients with moderate CKD and an eGFR ≥30 ml/min per 1.73 m^2.[27]

Although the effect of cardioprotection with metformin use is studied mainly in the general population, evidence of this benefit in patients with CKD, especially those with reduced eGFR, is less consistent. A systematic review considered the association of all-cause mortality and MACE with treatment regimens that included metformin in patient populations for which metformin use is traditionally taken with precautions.[28] There were no RCTs, and only observational studies were included in the analysis of the CKD cohort. All-cause mortality was found to be 22% lower for patients on metformin treatment than for those not receiving it (HR: 0.78; 95% CI: 0.63–0.96), whereas there was no difference in MACE-related diagnoses with metformin use in one study. However, a second study that had examined MACE outcomes with metformin use suggested that metformin treatment was associated with a slightly lower readmission rate for congestive heart failure (HR: 0.91; 95% CI: 0.84–0.99). Although the signal for cardioprotection in the CKD cohort appears to be poor, the lackluster quality of the evidence and the observational nature of the studies in this population preclude any definitive conclusion on the cardiovascular benefits with metformin treatment in patients with reduced eGFR.

Quality of the evidence

A search of the Cochrane Kidney and Transplant Registry identified no RCTs that had been conducted to evaluate the use of metformin in patients with T2D and CKD assessing cardiovascular and kidney protection as primary outcomes. The evidence that forms the basis of this clinical recommendation is extracted from RCTs and systematic reviews performed in the general population. The Work Group also considered the outcomes of studies that included patients with T2D and CKD, which were all observational in nature.

Values and preferences

The efficacy of HbA1c reduction, the good safety profile including a lower risk of hypoglycemia, and the low cost of metformin were judged to be critically important to patients. The Work Group assessed the benefit of weight reduction compared to use of insulin and sulfonylurea to be an important consideration, and patients who value weight reduction would prefer to be treated with metformin

compared to having no treatment or other treatments. In addition, being widely available at low cost would make metformin a relevant initial treatment option in low-resource settings.

Resources and other costs

Metformin is among the least-expensive antiglycemic medications available and is widely available. In resource-limited settings, this drug is affordable and may be the only drug available.

Considerations for implementation

Dose adjustments of metformin are required with a decline in the eGFR, and there is currently no safety data for metformin use in patients with an eGFR <30 ml/min per 1.73 m^2 or in those who are on dialysis. Patients will, therefore, need to be switched off metformin when the eGFR falls below 30 ml/min per 1.73 m^2. These practical issues will be addressed in the practice points.

Different formulations of metformin

Typically, metformin monotherapy has been shown to lower HbA1c by approximately 1.5%.[29, 30] Figure 26 outlines the different formulations, and their respective recommended doses, of metformin available.

Metformin is generally well-tolerated, although gastrointestinal adverse events may be experienced in up to 25% of patients treated with the immediate-release form of metformin, with treatment discontinuation occurring in about 5%–10% of patients.[31-33] Clinical studies have demonstrated that the tolerability of extended-release metformin was generally comparable to or even increased compared to the immediate-release formulation. In a 24-week double-blind RCT of adults with T2D who were randomly assigned to 1 of 3 extended-release metformin treatment regimens (1500 mg once daily, 1500 mg twice daily, or 2000 mg once daily) or immediate-release metformin (1500 mg twice daily), overall incidence of adverse events was noted to be similar for all treatment groups, although fewer patients in the extended-release group developed nausea during the initial dosing period (2.9%, 3.9%, and 2.4% for the respective extended-release treatment regimens vs. 8.2% in the immediate-release group, P = 0.05).[34] Moreover, fewer patients who received the extended-release metformin discontinued treatment because of gastrointestinal side effects during the first week (0.6% vs. 4.0%). Another RCT of 532 treatment-naïve Chinese patients with T2D (the CONSENT study), however, showed comparable gastrointestinal adverse events between a patient receiving monotherapy with immediate-release or extended-release metformin (23.8% vs. 22.3%, respectively).[35]

In view of the overall benefits of metformin treatment, and the possibility of improved tolerability of extended-release metformin, patients who experienced significant gastrointestinal side effects from the immediate-release formulation could be considered for a switch to extended-release metformin and monitored for improvement of symptoms.

Figure 26. Difference formulations of metformin

Formulation	Dosage forms	Starting dose	Maximum dose
Metformin, immediate release	Tablet, oral: 500 mg, 850 mg, 1000 mg	500 mg once or twice daily OR 850 mg once daily	Usual maintenance dose: 1 g twice daily OR 850 mg twice daily Maximum: 2.55 g/d
Metformin, extended release	Tablet, oral: 500 mg, 750 mg, 1000 mg	500 mg once daily OR 1 g once daily	2 g/d

Rationale

This recommendation places a higher value on the many potential advantages of metformin use in the general population, which include its efficacy in lowering HbA1c, its benefits in weight reduction and cardiovascular protection, its good safety profile, the general familiarity with the drug, its widespread availability and low cost; and a lower value on the lack of evidence that metformin has any renoprotective effects or mortality benefits.

This is a strong recommendation, as the Work Group judged that metformin would likely be the initial drug of choice for all or nearly all well-informed patients, due to its widespread availability and low cost, especially in low-resource settings. The Work Group also judged that the majority of physicians, if not all, will be comfortable in initiating metformin treatment due to familiarity with this drug, and its good safety profile.

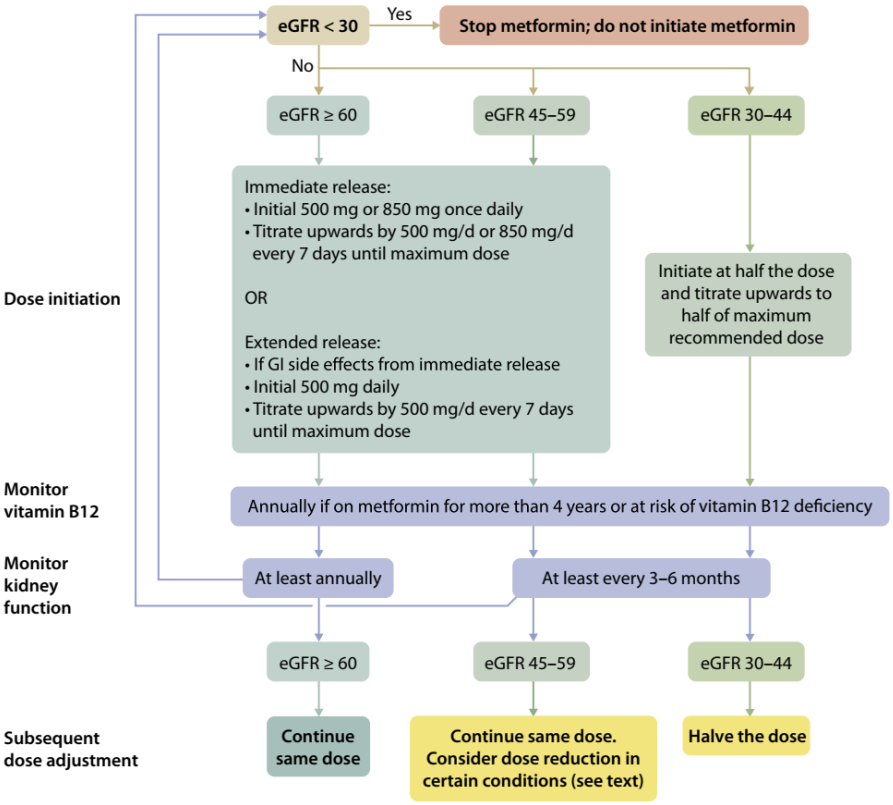
Practice Point 4.1.1: Treat kidney transplant recipients with T2D and an eGFR ≥30 ml/min per 1.73 m^2 with metformin according to recommendations for patients with T2D and CKD.

The data for the use of metformin after kidney transplantation are less robust. Most of the evidence was derived from registry and pharmacy claims data, which showed that the use of metformin was not associated with worse patient or allograft survival.[36] One such analysis even suggested that metformin treatment after kidney transplantation was associated with significantly lower all-cause, malignancy-related, and infection-related mortality.[37] The Transdiab study was a pilot, randomized, placebo-controlled trial that recruited 19 patients with impaired glucose tolerance after kidney transplantation from a single center, which examined the efficacy and tolerability of metformin treatment.[38] Although there were no adverse signals from the trial, the number of patients recruited unfortunately was too small for any conclusive recommendations. In view of the lack of data against the use of metformin after transplantation, it is the judgment of the Work Group that the recommendation for metformin use in the transplant population be based on the eGFR, using the same approach as for the CKD group.

Practice Point 4.1.2: Monitor eGFR in patients treated with metformin. Increase the frequency of monitoring when the eGFR is <60 ml/min per 1.73 m^2 (Figure 27).

Given that metformin is excreted by the kidneys and there is concern for lactic acid accumulation with a decline in kidney function, it is important to monitor the eGFR at least annually when a patient is on metformin treatment. The frequency of monitoring should be increased to every 3–6 months as the eGFR drops below 60 ml/min per 1.73 m^2, with a view to decreasing the dose accordingly.

Figure 27. Suggested approach in dosing metformin based on the level of kidney function


eGFR < 30
Yes
Stop metformin; do not initiate metformin
No
eGFR ≥ 60
eGFR 45–59
eGFR 30–44
Dose initiation
Immediate release:
• Initial 500 mg or 850 mg once daily
• Titrate upwards by 500 mg/d or 850 mg/d every 7 days until maximum dose
OR
Extended release:
• If GI side effects from immediate release
• Initial 500 mg daily
• Titrate upwards by 500 mg/d every 7 days until maximum dose
Initiate at half the dose and titrate upwards to half of maximum recommended dose
Monitor vitamin B12
Annually if on metformin for more than 4 years or at risk of vitamin B12 deficiency
Monitor kidney function
At least annually
At least every 3–6 months
eGFR ≥ 60
eGFR 45–59
eGFR 30–44
Subsequent dose adjustment
Continue same dose
Continue same dose. Consider dose reduction in certain conditions (see text)
Halve the dose

eGFR, estimated glomerular filtration rate (in ml/min per 1.73 m^2); GI, gastrointestinal

Practice Point 4.1.3: Adjust the dose of metformin when the eGFR is <45 ml/min per 1.73 m^2, and for some patients when the eGFR is 45–59 ml/min per 1.73 m^2 (Figure 27).

Figure 27 provides a suggested approach in adjusting the dose for metformin in accordance to the decline in kidney function:

- For an eGFR between 45–59 ml/min per 1.73 m^2, dose reduction may be considered in the presence of conditions that predispose patients to hypoperfusion and hypoxemia.
- The maximum dose should be halved when the eGFR declines to between 30–45 ml/min per 1.73 m^2.
- Treatment should be discontinued when the eGFR declines to <30 ml/min per 1.73 m^2, or when the patient is initiated on dialysis, whichever is earlier.

Practice Point 4.1.4: Monitor patients for vitamin B12 deficiency when they are treated with metformin for more than 4 years.

Metformin interferes with intestinal vitamin B12 absorption, and the NHANES found that biochemical vitamin B12 deficiency was noted in 5.8% of patients with diabetes on metformin, compared to 2.4% (P= 0.0026) in those not on metformin, and 3.3% (P = 0.0002) in patients without diabetes.[39] One study randomized patients with T2D on insulin to receive metformin or placebo and examined the development of vitamin B12 deficiency over a mean follow-up period of 4.3 years.[40] Metformin treatment was associated with a mean reduction of vitamin B12 concentration compared to

placebo after approximately 4 years. However, clinical consequences of vitamin B12 deficiency with metformin treatment are uncommon, and it is the judgment of the Work Group that routine concurrent supplementation with vitamin B12 is unnecessary. In addition, the study demonstrated that the reduction in vitamin B12 concentration is increased with time of metformin therapy. Monitoring of vitamin B12 levels should be considered in patients who have been on long-term metformin treatment (e.g., >4 years) or in those who are at risk of low vitamin B12 levels (e.g., patients with malabsorption syndrome, or reduced dietary intake [vegans]).

Research recommendations

RCTs are needed to:

- Evaluate the safety, efficacy, and potential cardiovascular and renoprotective benefits of metformin use in patients with T2D and CKD, including those with an eGFR <30 ml/min per 1.73 m^2 or on dialysis.
- Evaluate the safety and efficacy of metformin in kidney transplant recipients.

4.2 Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

GLP-1 is an incretin hormone secreted from the intestine after ingestion of glucose or other nutrients. In the pancreas, it stimulates glucose-dependent release of insulin from beta cells and suppresses glucagon release from alpha cells. GLP-1 also slows gastric emptying and decreases appetite stimulation in the brain, facilitating weight loss. These incretin effects are reduced or absent in patients with diabetes.

Long-acting GLP-1 RA medications, which stimulate this pathway, have been shown to substantially improve glycemic control and confer weight loss. More importantly, though, several GLP-1 RA agents have been shown to reduce MACE in patients with T2D with HbA1c >7.0%, who were at high cardiovascular risk.[1-4] Additionally, these same GLP-1 RA agents have been shown to have kidney benefits by reductions in albuminuria and slowing the rate of eGFR decline.[3-6]

Recommendation 4.2.1: In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, we recommend a long-acting GLP-1 RA (1B).

This recommendation places a high value on the cardiovascular and kidney benefits of long-acting GLP-1 RA treatment in patients with T2D and CKD, and a lower value on the costs and adverse effects associated with this class of drug.

Key information

Balance of benefits and harms

Data for cardiovascular, kidney outcomes, and cardiometabolic benefits are summarized below.

Cardiovascular outcomes

There are currently 6 published large RCTs examining cardiovascular outcomes for injectable GLP-1 RA[15, 41-51] and 1 trial of an oral GLP-1 RA (Figure 28).[52] Of these, 5 studies (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER],[46] Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes [SUSTAIN-6],[47] Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus [HARMONY],[53], Researching Cardiovascular Events With a Weekly Incretin in Diabetes [REWIND][43], and Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O)[15]) have confirmed cardiovascular benefit of 4 injectable GLP-1 RA with significant reductions in MACE for liraglutide, semaglutide, albiglutide, dulaglutide, and efpeglenatide, respectively. The other agents (lixisenatide, exenatide, and oral semaglutide) have been shown to have cardiovascular safety, but without significant effects on cardiovascular risk reduction.

The LEADER trial (evaluating liraglutide) included 9340 individuals with T2D and HbA1c ≥7% with high cardiovascular risk defined as established CVD, G3 CKD or higher, age ≥60 years, or a major CVD risk factor.[46] Of note, the LEADER trial also included 220 individuals with an eGFR of 15–30 ml/min per 1.73 m^2. The LEADER trial compared once-daily liraglutide to placebo and followed participants for a median of 3.8 years for primary MACE outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. There was a 13% reduction in MACE (HR: 0.87; 95% CI: 0.78–0.97) conferred by liraglutide.

In the LEADER trial, the risk reduction for the primary composite MACE outcome was even greater among individuals with CKD G3a or greater severity (eGFR <60 ml/min per 1.73 m^2) compared to those with an eGFR ≥60 ml/min per 1.73 m^2 (HR: 0.69; 95% CI: 0.57–0.85 vs. HR: 0.94; 95% CI: 0.83–1.07, respectively, *P*-interaction = 0.01).[54] This benefit was seen across each separate cardiovascular outcome. Notably, liraglutide (compared to placebo) conferred an impressive 49% reduction for nonfatal stroke with HR: 0.51 (95% CI: 0.33–0.80) for eGFR <60 ml/min per 1.73 m^2 versus HR: 1.07 (95% CI: 0.84–1.37) for eGFR ≥60 ml/min per 1.73 m^2. Although subgroup analyses should be considered cautiously, these findings suggest that efficacy among individuals with CKD is at least as great as that for those without CKD.

The SUSTAIN-6 trial (evaluating injectable semaglutide) enrolled 3297 patients with T2D and HbA1c ≥7% with CVD, CKD G3 or higher, or age ≥60 years with at least 1 major CVD risk factor.[47] A total of 83% of participants had CVD, CKD, or both, with 10.7% having CKD only and 13.4% having both CKD and CVD. SUSTAIN-6 found that once-weekly semaglutide compared to placebo reduced the primary composite MACE outcome by 26% (HR: 0.74; 95% CI: 0.58–0.95). In subgroup analysis, there was no evidence of effect heterogeneity by CKD subgroup with similar MACE reduction for those with an eGFR <30 ml/min per 1.73 m^2 versus ≥30 ml/min per 1.73 m^2 (*P*-interaction = 0.98) and similar reduction for those with an eGFR <60 ml/min per 1.73 m^2 versus ≥60 ml/min per 1.73 m^2 (*P*-interaction = 0.37).

The HARMONY trial (evaluating albiglutide) evaluated 9463 participants with T2D and high cardiovascular risk with HbA1c ≥7%.[44] Of note, an eGFR <30 ml/min per 1.73 m^2 was an exclusion criterion. HARMONY found that albiglutide (dosed once weekly) compared to placebo reduced the primary MACE outcome (cardiovascular death, myocardial infarction, or stroke) over a median duration of follow-up of 1.6 years in the overall cohort by 22% (HR: 0.78; 95% CI: 0.68–0.90). There

was no significant heterogeneity of treatment benefit for the primary cardiovascular outcome among the eGFR subgroups of <60 ml/min per 1.73 m^2, ≥60–90 ml/min per 1.73 m^2, and ≥90 ml/min per 1.73 m^2 (*P*-interaction = 0.19). At this time, albiglutide is currently not available on the market, so this is not an option for patients.

The REWIND trial (evaluating dulaglutide) included 9901 adults with T2D with HbA1c of ≤9.5% (with no lower limit and mean HbA1c of 7.2%).[43] An eGFR <15 ml/min per 1.73 m^2 was an exclusion criterion. The REWIND trial enrolled a low proportion of patients with established CVD (31.5%); thus, it is largely considered a primary prevention trial. The REWIND trial also included a significant number of individuals with CKD. Over a median follow-up of 5.4 years, the primary MACE outcome (composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or CVD death) was 12% lower with once-weekly dulaglutide compared to placebo (HR: 0.88; 95% CI: 0.79–0.99). The reduction in primary cardiovascular outcome was similar among those with and without previous CVD (*P*-interaction = 0.97).

In contrast, the Evaluation of LIXisenatide in Acute Coronary Syndrome (ELIXA; lixisenatide)[50] and the EXenatide Study of Cardiovascular Event Lowering (EXSCEL; exenatide)[41, 45] trials did not show a cardiovascular benefit with GLP-1 RA, nor did they find increased harm, confirming cardiovascular safety. Differences in the results of the ELIXA and EXSCEL trials, compared with the more favorable results seen in the LEADER, SUSTAIN, HARMONY, and REWIND trials may stem from differences in GLP-1 RA molecular structures, half-lives, and formulations, study design, or the patient populations studied. For example, the ELIXA trial had a high discontinuation and dropout rate.

Finally, the Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 study investigated the cardiovascular safety of an oral GLP-1 RA (oral semaglutide).[52] The study evaluated 3183 patients with T2D and high cardiovascular risk, CKD, or age >50 years with a major CVD risk factor. An eGFR <30 ml/min per 1.73 m^2 was an exclusion criterion. Oral semaglutide was found to not be inferior to placebo for primary MACE outcomes. Furthermore, there was no difference in the primary outcome for participants with an eGFR <60 ml/min per 1.73 m^2 versus ≥60 ml/min per 1.73 m^2 (*P*-interaction = 0.80), with HR for primary outcome of 0.74 (95% CI: 0.41–1.33) for those with an eGFR <60 ml/min per 1.73 m^2.

A 2021 meta-analysis of the 8 trials of GLP-1 RA (ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, PIONEER 6, and AMPLITUDE-O), which together included a total of 60,080 participants, evaluated pooled cardiovascular and kidney outcome data in participants with T2D, including those with CKD.[55] Compared to placebo, GLP-1 RA treatment conferred a reduction in cardiovascular death (HR: 0.87; 95% CI: 0.80–0.94), stroke (HR: 0.83; 95% CI: 0.76–0.92), myocardial infarction (HR: 0.90; 95% CI: 0.83–0.98), all-cause mortality (HR: 0.88; 95% CI: 0.82–0.94), and hospitalization for heart failure (HR: 0.89; 95% CI: 0.82–0.98). Of note, this is the first time a benefit for heart failure hospitalization has been demonstrated for the GLP-1 RA class of medications.

Kidney outcomes

The LEADER trial also examined the effects of liraglutide compared to placebo on a prespecified secondary composite kidney outcome (new-onset severely increased albuminuria, doubling of serum creatinine, kidney failure, or death from kidney disease).[46] Liraglutide conferred a significant 22% reduction in this composite kidney outcome (HR: 0.78; 95% CI: 0.67–0.92), driven primarily by reduction in new-onset severely increased albuminuria (HR: 0.74; 95% CI: 0.60–0.91). There was no difference between liraglutide and placebo in serum creatinine or kidney failure, and few deaths attributed to kidney disease occurred in the study.

In the SUSTAIN-6 trial, there was also a reduction in new or worsening nephropathy with semaglutide compared to placebo (HR: 0.64; 95% CI: 0.46–0.88).[47] This composite kidney outcome

included persistent severely increased albuminuria, persistent doubling of serum creatinine, a creatinine clearance of <45 ml/min, or need for kidney replacement therapy.

The REWIND trial also examined dulaglutide's benefit on CKD as a component of the secondary microvascular outcome.[42] There was a 15% reduction in the composite kidney outcome defined as new severely increased albuminuria (ACR of >33.9 mg/mmol [339 mg/g]), sustained eGFR decline of 30% from baseline, or use of kidney replacement therapy with dulaglutide compared to placebo (HR: 0.85; 95% CI: 0.77–0.93). Similar to other GLP-1 RA trials, the strongest evidence for benefit was for new severely increased albuminuria (HR: 0.77; 95% CI: 0.68–0.87). Notably, in *post hoc* exploratory analyses, eGFR decline thresholds of 40% and 50% were significantly reduced by 30% and 46%, respectively. Of course, exploratory results must be interpreted cautiously and regarded as hypothesis-generating. There were no serious adverse events for kidney disease in the REWIND trial. Among the 9901 participants, 22.2% had an eGFR <60 ml/min per 1.73 m^2 at baseline, and 7.9% had severely increased albuminuria. The benefit on the composite kidney outcome was similar among those with an eGFR ≥60 ml/min per 1.73 m^2 or <60 ml/min per 1.73 m^2 (*P*-interaction = 0.65), and among subgroups defined by baseline albuminuria status and use of an ACEi or ARB. Of note, the HbA1c-lowering and blood pressure–lowering effects explained 26% and 15%, respectively, of the kidney benefits conferred by dulaglutide. Hence, not all of the benefit of GLP-1 RA can be explained by improvement in conventional CKD risk factors.

Another important study that supports a potential kidney benefit and emphasizes the safety of a GLP-1 RA for glycemic control in the CKD population was the Assessment of Weekly Administration of LY2189265 (Dulaglutide) in Diabetes 7 (AWARD-7) trial, which compared dulaglutide to insulin glargine among patients with moderate-to-severe CKD.[51] Although glycemic indices were the primary outcome of the trial, kidney outcomes (eGFR and ACR) were the main secondary outcomes. AWARD-7 enrolled patients with T2D and CKD G3a–G4 (mean eGFR 38 ml/min per 1.73 m^2) who were being treated with an ACEi or ARB and found that dulaglutide conferred significantly less eGFR decline over 52 weeks (mean: –3.3 ml/min per 1.73 m^2 vs. –0.7 ml/min per 1.73 m^2) with either a lower dose (0.75 mg weekly) or higher dose (1.5 mg weekly) of dulaglutide, respectively, compared to insulin glargine. The benefits on eGFR were most evident in the severely increased albuminuria subgroup (mean: –5.5 ml/min per 1.73 m^2 vs. –0.7 ml/min per 1.73 m^2 and –0.5 ml/min per 1.73 m^2 over 52 weeks) with the lower and higher doses of dulaglutide, respectively. These benefits were accomplished with similar improvement in HbA1c (mean 1%) and comparable blood pressure levels between the dulaglutide and insulin glargine groups. Notably, rates of symptomatic hypoglycemia were reduced by half with dulaglutide compared to insulin glargine. Although there were the expected higher rates of gastrointestinal side effects, the overall safety profile of dulaglutide was confirmed in CKD G3a–G4. As a result, dulaglutide has received FDA approval for glycemic control in T2D with eGFR as low as 15 ml/min per 1.73 m^2. In a pre-specified exploratory analysis of AWARD-7, risk for 40% eGFR decline or kidney failure treated by dialysis or kidney transplant was reduced by more than half, and in those with macroalbuminuria, the relative risk for this outcome was reduced by 75% (HR 0.25; 95 % CI 0.10-0.68).[56]

In the 2021 meta-analysis of 8 cardiovascular outcomes trials (ELIXA, LEADER, SUSTAIN-6, EXSCEL, HARMONY, REWIND, and PIONEER-6, AMPLITUDE-O), GLP-1 RA treatment reduces risk for a broad composite kidney outcome (development of new severely increased albuminuria, decline in eGFR, or rise in serum creatinine, progression to kidney failure, or death from kidney disease cause; HR: 0.79; 95% CI: 0.73–0.87) compared to placebo in populations with T2D.[14] In these groups selected for high CVD risk, kidney endpoints were driven largely by reduction in albuminuria as to be expected. Excluding severely increased albuminuria, the association of GLP-1 RA with worsening kidney function did not achieve statistical significance, but the signal points toward benefit (HR: 0.86; 95% CI: 0.72–1.02).[14]

A major limitation is that results have not been reported from a clinical trial enrolling a study population selected for CKD or in which kidney outcomes were the primary outcome. However, a clinical trial of GLP-1 RA with a primary kidney disease outcome is forthcoming with the ongoing Effect of Semaglutide Versus Placebo on the Progression of Renal Impairment in Subjects With Type 2 Diabetes and Chronic Kidney Disease (FLOW) trial (NCT03819153) that is evaluating whether injectable semaglutide 1 mg weekly among patients with T2D and an eGFR of 25–50 ml/min per 1.73 m^2 or with severely increased albuminuria on a background of ACEi or ARB therapy confers kidney benefit. A companion mechanistic trial, the Renal Mode of Action of Semaglutide in Patients With Type 2 Diabetes and Chronic Kidney Disease study (REMODEL, NCT04865770) is examining effects of semaglutide on kidney inflammation, perfusion, and oxygenation by magnetic resonance imaging and kidney biopsies.[57]

Figure 28. Cardiovascular and kidney outcome trials for GLP-1 RA

	ELIXA	LEADER	SUSTAIN	EXSCEL	HARMONY	REWIND	PIONEER 6	AMPLITUDE-O	AWARD-7
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide (oral)	Efpeglenatide	Dulaglutide
Total number of participants	6068	9340	3297	14,752	9463	9901	3183	4076	577
% with CVD	100	81.3	83	73	100	31.5	84.7	89.6	Not reported
eGFR criteria for enrollment (ml/min per 1.73 m²)	≥30	Most had eGFR ≥30, but did include 220 patients with eGFR 15 to 30	Not reported	≥30	≥30	≥15	≥30 (however 0.9% had eGFR <30)	25–59.9	Not reported
Mean eGFR at enrollment (ml/min per 1.73 m²)	76	80	~75	76	79	76.9	74	72.4	38
% with eGFR <60 ml/min per 1.73 m²	23	20.7 with eGFR 30 to 59 ml/min per 1.73 m², 2.4 with eGFR <30 ml/min per 1.73 m²	28.5	22.9	Not reported	22.2	26.9	31.6	100 with CKD G3a–G4
ACR	19% with moderately increased albuminuria and 7% with severely increased albuminuria	Not reported	Not reported	3.5% with severely increased albuminuria	Not reported	7.9% with severely increased albuminuria	Not reported	Median 28.3 mg/g [2.83 mg/mmol]	44% with severely increased albuminuria
Follow-up time (yr)	2.08	3.8	2.1	3.2	1.6	5.4	1.36	1.81	1
CV outcome definition	CV death, MI, stroke, or hospitalization for unstable angina	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	MACE	NA
CV outcome results	HR: 1.02; 95% CI: 0.89–1.17	HR: 0.87; 95% CI: 0.78–0.97	HR: 0.74; 95% CI: 0.58–0.95	HR: 0.91; 95% CI: 0.83–1.00	HR: 0.78; 95% CI: 0.68–0.90	HR: 0.88; 95% CI: 0.79–0.99	HR: 0.79; 95% CI: 0.57–1.11	HR: 0.73; 95% CI: 0.58–0.92	NA
Kidney outcome (secondary end points)	New-onset severely increased albuminuria and doubling of SCr	New-onset persistent severely increased albuminuria, persistent doubling of the SCr level, kidney failure, or death due to kidney disease	Persistent severely increased albuminuria, persistent doubling of SCr, a CrCl of <45 ml/min, or need for KRT	Two kidney composite outcomes: 1) 40% eGFR decline, kidney replacement, or renal death, 2) 40% eGFR decline, kidney replacement, renal death, or severely increased albuminuria	Not reported	New severely increased albuminuria ACR of >33.9 mg/mmol [339 mg/g], a sustained fall in eGFR of 30% from baseline, or use of KRT	Not reported	Composite of incident severely increased albuminuria (ACR >300 mg/g or >33.9 mg/mmol), increase in ACR ≥30%, sustained decrease in eGFR by ≥40% for ≥30 days, or kidney replacement therapy for ≥90 days, or a sustained eGFR of <15 ml/min per 1.73 m² for ≥30 days	eGFR, ACR
Kidney outcome results	New-onset macroalbuminuria: adjusted HR: 0.81; 95% CI: 0.66–0.99, *P*=0.04; Doubling of SCr: adjusted HR: 1.16; 95% CI: 0.74–1.83, *P*=0.51	HR: 0.78; 95% CI: 0.67–0.92	HR: 0.64; 95% CI: 0.46–0.88	40% eGFR decline, kidney replacement, or renal death: adjusted HR: 0.87; 95% CI: 0.73–1.04, *P*=0.13; 40% eGFR decline, kidney replacement, renal death, or severely increased albuminuria: adjusted HR: 0.85; 95% CI: 0.74-0.98, *P*=0.03	Not reported	HR: 0.85; 95% CI: 0.74–0.98 Similar for eGFR ≥60 vs. <60 ml/min per 1.73 m², no albuminuria vs. albuminuria, no ACEi/ARB vs. ACEi/ARB	Not reported	Kidney composite outcome: HR: 0.68; 95% CI: 0.57–0.79	eGFR did not significantly decline (0.7 ml/min per 1.73 m²) with dulaglutide 1.5 mg or dulaglutide 0.75 mg, whereas eGFR decreased by –3.3 ml/min per 1.73 m² with insulin glargine

ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin–creatinine ratio; ARB, angiotensin II receptor blocker; CrCl, creatinine clearance; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (ml/min per 1.73 m^2); G, glomerular filtration rate category; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; KRT, kidney replacement therapy; MI, myocardial infarction; NA, not available; SCr, serum creatinine

Cardiometabolic benefits

The favorable effects of GLP-1 RA on risk factors (i.e., reductions in glycemia, blood pressure, and body weight) may contribute to the favorable cardiovascular and CKD outcomes versus placebo or insulin therapy. GLP-1 RA are more potent glucose-lowering agents compared to SGLT2i in the CKD population and confer greater weight-loss potential.

Harms

Most GLP-1 RA are administered subcutaneously. Some patients may not wish to take an injectable medication. There is currently 1 FDA-approved oral GLP-1 RA (semaglutide).

Side effects of GLP-1 RA may preclude use of a GLP-1 RA in some patients. There is risk of adverse gastrointestinal symptoms (nausea, vomiting, and diarrhea). The gastrointestinal side effects are dose-dependent and may vary across GLP-1 RA formulations.[58] There also might be injection-site reactions and an increase in heart rate with this therapy, and GLP-1 RA should be avoided in patients at risk for thyroid C-cell (medullary thyroid) tumors and with a history of acute pancreatitis.

Low eGFR dose adjustment is required for exenatide and lixisenatide. However, given that the ELIXA[50] and EXSCEL[45, 59] trials did not prove any cardiovascular benefit with these agents, the priority would be to use one of the other available GLP-1 RA, which have shown CVD and CKD benefits (i.e., liraglutide, semaglutide, and dulaglutide). Notably, effects of GLP-1 RA on cardiovascular and CKD outcomes appear not to be entirely mediated through improved risk factors. Treatment with GLP-1 RA may be used for heart and kidney protection as well as to manage hyperglycemia. Initiation of a GLP-1 RA must take into account other glucose-lowering agents, especially those associated with hypoglycemia, which may require changes to these medications. Of note, in the largest meta-analyses conducted to date with 8 GLP-1 RA trials including 60,080 participants, there were no increased risks of hypoglycemia, pancreatitis, or pancreatic cancer.[14]

Although GLP-1 RA and SGLT2i reduce MACE to a similar degree, GLP-1 RA may be preferred for ASCVD, whereas there is currently stronger evidence for SGLT2i for reduction in heart failure and CKD progression. For patients with T2D, CKD, and an eGFR ≥20 ml/min per 1.73 m^2, SGLT2i agents are preferred over GLP-1 RA as initial heart and kidney protective agents. However, in light of the aforementioned beneficial effects of GLP-1 RA on cardiovascular and kidney outcomes in patients with T2D, GLP-1 RA are an excellent addition for patients who have not achieved their glycemic target or as an alternative for patients unable to tolerate metformin and/or an SGLT2i. GLP-1 RA may also be useful for reducing albuminuria.

GLP-1 RA are contraindicated for patients with a history of medullary thyroid cancer or with multiple endocrine neoplasia 2 (MEN-2), although these are rare conditions, and for patients with a history of acute pancreatitis.

In summary, the overall safety data for liraglutide, semaglutide, albiglutide, and dulaglutide, efpeglenatide from the LEADER, SUSTAIN 6, HARMONY, REWIND, AWARD-7, and APMPLITUDE-O clinical trials are acceptable, and the cardiovascular benefits are considerable with additional benefits conferred for kidney outcomes.

Quality of evidence

The overall quality of the evidence was rated as moderate. This recommendation comes from double-blinded, placebo-controlled RCTs of GLP-1 RA that enrolled patients with CKD,[15, 41, 43-48, 50-54, 60-66] a meta-analysis of these 7 RCTs combining efficacy data for cardiovascular and kidney outcomes,[55] and an update to the 2018 Cochrane systematic review and meta-analysis[6] in patients with diabetes and CKD conducted by the ERT (Supplementary Table S23[15, 43-45, 47-49, 51-53, 59, 60, 66-71]). From these data, there is moderate quality of evidence that GLP-1 RA reduce MACE among patients with T2D. The

quality of the evidence was downgraded to moderate because of the inconsistency of the data, with an I^2 of 55%, with some studies demonstrating benefit and others little to no difference of GLP-1 RA compared to placebo/standard of care.

There also appears to be favorable benefits in broad composite kidney outcomes, largely driven by reduction in severely increased albuminuria, with less evidence to support benefit for harder kidney outcomes (Supplementary Table S23[15, 43-45, 47-49, 51-53, 59, 60, 66-71]). There also has not been a designated trial published to date with a primary endpoint of kidney outcomes, although the ongoing FLOW trial (NCT03819153) will determine whether GLP-1 RA can slow progression of CKD in T2D.

- *Study design:* There have now been multiple RCTs, with an adequate number of study participants, that have evaluated the benefit of GLP-1 RA on clinically meaningful cardiovascular outcomes. CKD outcomes have been examined as either predefined secondary outcomes or exploratory outcomes. As discussed above, a systematic review and meta-analysis of RCTs confirmed evidence of benefit for important major cardiovascular outcomes, as well as broad kidney composite outcome, largely driven by reduction in urinary albumin excretion.[14]
- *Risk of bias:* The risk of bias is low as the 7 large RCTs studies demonstrated good allocation concealment and adequate blinding, with complete accounting for all patients and outcome events. In the aforementioned meta-analysis of 7 RCTs of GLP-1 RA, the authors found that all trials were of high quality and met criteria for low risk of bias as assessed by the Cochrane Risk of Bias tool.[55] However, in the updated Cochrane review focused on people with diabetes and CKD, found unclear reporting of allocation concealment and blinding in other included trials which downgraded the quality of evidence for hypoglycemia requiring 3rd party assistance, hyperkalemia, HbA1c, eGFR loss, change in body weight, and body mass index.
- *Consistency:* The consistency is moderate to high across the trials. In the analysis of patients with CKD, heterogeneity was observed for the primary cardiovascular outcome (3-point MACE) (I^2=55%). No heterogeneity was observed for secondary kidney outcomes across baseline eGFR and baseline ACR groups. Other important outcomes such as, HbA1c (I^2=86%) and eGFR loss (I^2=70%) also demonstrated a high heterogeneity.
- *Indirectness:* The RCT studies directly compared the effect of GLP-1 RA with placebo, with other potential confounding clinical variables generally being well-distributed between the treatment and control arms. One study was an active comparator trial with comparable glycemic and blood pressure control between GLP-1 RA– and insulin-treated groups.
- *Precision:* For critical and important outcomes, the precision is good, as the studies conducted included large numbers of study participants with acceptable event rates. Although, in participants with CKD and diabetes, there were fewer events and some outcomes (AKI and hyperkalemia) did not exclude minimally clinical important difference. Hence, these outcomes have been downgraded due to serious imprecision.
- *Publication bias*: All the published RCTs were registered at clinicaltrials.gov. The majority of studies were commercially funded, but overall, there was no evidence of undue industry influence on the included RCT findings.

Values and preferences

The Work Group judged that the majority of well-informed patients with T2D and CKD who cannot take an SGLT2i because of tolerance or a contraindication would choose to receive a GLP-1 RA because of the cardiovascular benefits associated with this class of medications. Patients with or at high risk for ASCVD or with residual albuminuria who need further glycemic management might be particularly inclined to choose a GLP-1 RA. In contrast, patients who experience severe gastrointestinal

side effects or are unable to administer an injectable medication, or those for whom GLP-1 RA are unaffordable or unavailable, will be less inclined to choose these agents.

Resource use and costs

Although some models have found the use of GLP-1 RA to be a cost-effective strategy among patients with T2D,[72, 73] these medications are frequently cost-prohibitive for many patients compared to other oral glucose-lowering agents (e.g., sulfonylureas), which do not have evidence for cardiovascular and kidney benefits. In many cases in the US, obtaining preauthorization from insurance companies for GLP-1 RA place an undue burden on health care professionals and patients. Even with insurance coverage, many patients are still faced with a large copayment.

Availability of drugs also varies among countries and regions. Thus, treatment decisions must take into account the patient's preference, drug availability in the country, and cost. Ultimately, patients may need to choose between the cost of these medications versus their anticipated benefits, and some patients may not be able to access them.

Considerations for implementation

For patients with T2D and CKD, the Work Group recommends prioritizing, after lifestyle measures, metformin and an SGLT2i as initial glucose-lowering and organ protective medication. For patients unable to take or tolerate these medications, or if additional glycemic management is needed, these guidelines then recommend prioritizing GLP-1 RA over other glucose-lowering agents, given their established cardiovascular and potential kidney benefits (Figure 23). This approach is consistent with the recommendations from other professional societies, including the ACC,[74] ADA,[75, 76] and ESC/EASD.[77]

Patients with T2D and CKD benefited from GLP-1 RA therapy in RCTs. In subgroup analysis from the conducted trials of GLP-1 RA therapy in patients with T2D and CKD, the cardiovascular benefits were sustained independent of age, sex, and race/ethnicity. Thus, this recommendation holds for all patients. However, long-term follow-up and ongoing collection of real-world data are needed to validate effectiveness and potential harms.

This recommendation applies to kidney transplant recipients, as there is no evidence to indicate different outcomes in this population. Conversely, there is less available safety data for patients with CKD G5 or on kidney replacement therapy, so caution should be exercised in these groups.[78] These medications may exacerbate gastrointestinal symptoms in peritoneal dialysis patients or those who are uremic or under-dialyzed, or those who have cachexia or malnutrition.

Practice Point 4.2.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

When the decision has been made to add a GLP-1 RA, given that the ELIXA (lixisenatide),[50] and EXSCEL (exenatide)[41, 45] trials did not prove cardiovascular benefit with these agents, and that albiglutide is currently unavailable, the priority would be to use one of the other GLP-1 RA, which have proven cardiovascular and kidney benefit (i.e., liraglutide, semaglutide [injectable], and dulaglutide). Additionally, cardiovascular benefit has not been demonstrated for oral semaglutide, as the PIONEER 6[52] trial was powered for only non-inferiority.

Patients with T2D and CKD are a heterogeneous group of patients, and treatment of hyperglycemia is complex. Treatment algorithms must be tailored to individuals, taking into consideration patient priorities and preferences, treatment availability, and cost, as part of shared decision-making.

Practice Point 4.2.2: To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly (Figure 29).

Figure 29. Dosing for available GLP-1 RA and dose modification for CKD

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with CrCl >30 ml/min
Liraglutide	0.6 mg, 1.2 mg, and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

CKD, chronic kidney disease; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist

Practice Point 4.2.3: GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.

DPP-4 inhibitors and GLP-1 RA should not be used together. Given that GLP-1 RA have been shown to have cardiovascular benefit, consideration may be given to stopping the gliptin medication (DPP-4) in order to facilitate treatment with a GLP-1 RA instead.

Practice Point 4.2.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA is used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.

GLP-1 RA are preferred over classes of glucose-lowering medications with less evidence supporting reduction of cardiovascular or kidney risks (e.g., DPP-4 inhibitors, thiazolidinediones, sulfonylureas, insulin, and acarbose). GLP-1 RA on their own do not cause hypoglycemia, but they may increase the risk of hypoglycemia caused by sulfonylureas or insulin when used concurrently. Therefore, it is reasonable to stop or reduce the dose of sulfonylurea or insulin when starting a GLP-1 RA if the combination may lead to an unacceptable risk of hypoglycemia.

Practice Point 4.2.5. GLP-1 RA may be preferentially used in patients with obesity, T2D, and CKD to promote intentional weight loss.

Persons with T2D and CKD often are obese even at advanced stages of CKD. Obesity has numerous adverse health effects, including higher risks of cardiovascular disease and CKD. These risks are mediated by "indirect" effects such as worsened risk factors (e.g., hyperglycemia, hypertension) as well as by "direct" effects of obesity (e.g., pro-inflammatory state, fat compression of organs).[79, 80] As a class GLP-1 RA have demonstrated weight loss. Both semaglutide and liraglutide have been studied and approved for weight loss in non-diabetic obesity.[81] In the AWARD-7 trial of patients with T2D and CKD G3a–G4, dulaglutide treatment (1.5 mg weekly) produced a mean weight loss of nearly 4 kg over one year, while insulin users gained >1 kg on average.[51] Thus, the weight differential between conventional insulin and dulaglutide treatment was about 5 kg after one year. This magnitude of weight

loss is clinically meaningful from the perspectives of improving cardiovascular and CKD risk factors and for heart and kidney protection. Furthermore, weight loss may be required to qualify people with obesity and advanced stages of CKD for kidney transplant. GLP-1 RA promotes weight loss in these individuals and can be valuable a tool to increase rates of pre-emptive and overall kidney transplants.

Research recommendations

- Future GLP-1 RA studies should consider evaluating kidney outcomes as the primary outcome.
- Future evidence should confirm clinical evidence of cardiovascular outcome and kidney benefit of GLP-1 RA among patients with T2D in a population selected for CKD, as prior studies have examined only CKD subgroups enrolled in the main trials.
- Future studies should focus on long-term (>5 years) safety and efficacy of using GLP-1 RA among patients with T2D and CKD. We need continued longer safety follow-up data and post-marketing surveillance including real-world evidence studies.
- Future studies should confirm the safety and clinical benefit of GLP-1 RA for patients with T2D with severe CKD, including those who are on dialysis, for whom there are limited data, and provide more data on CKD G4.
- Future studies should confirm the safety and clinical benefit of GLP-1 RA for patients with T2D and kidney transplant.
- Future studies should examine what biomarkers are appropriate to follow to assess the clinical benefit of GLP-1 RA (i.e., HbA1c, body weight, blood pressure, albuminuria, etc.).
- Although the REWIND trial provided encouraging results about the cardiovascular outcome benefit of GLP-1 RA among patients with T2D and CKD without established CVD (i.e., exclusively primary prevention population), more population or trial data would be useful to confirm their role, as most studies have focused on secondary prevention.
- Future studies should focus on kidney and heart protective benefits of GLP-1 RA, as well as their safety, for use in patients with T1D.
- Future studies should examine whether there are safety and efficacy issues of GLP-1 RA among individuals with a history of T2D and CKD who now have controlled HbA1c <6.5%. For example, among CKD patients at high risk for ASCVD, is there a benefit to using GLP-1 RA among individuals who are currently have good glycemic control?
- Future studies should report on the cost-effectiveness of a strategy that prioritizes adding a GLP-1 RA among patients with T2D and CKD, while factoring in cardiovascular and kidney benefits against the cost of medications and the potential for adverse effects.
- Future studies should further investigate whether the cardiovascular and kidney benefits are increased when GLP-1 RA are combined with SGLT2i treatment.[82]
- Future work should address how to better implement these treatment algorithms in clinical practice and how to improve availability and uptake in low-resource settings.

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Methods for guideline development

Aim

The aim of this project was to update evidence-based clinical practice guideline for the monitoring, prevention of disease progression, and treatment in patients with diabetes and CKD published in 2020.[1]

Overview of process

These guidelines adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3)[2, 3] and reported in accordance with the AGREE II reporting checklist.[4] The processes undertaken for the update of the *KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD* are described below.

- Defining the scope of the guidelines update
- Implementing literature search strategies to update the evidence base for the guidelines
- Selecting studies according to predefined inclusion criteria
- Conducting data extraction and critical appraisal of the literature
- Updating the evidence synthesis and meta-analysis to include newly identified studies
- Updating the certainty of the evidence for each outcome
- Finalizing guideline recommendations and supporting rationale
- Grading the strength of the recommendation, based on the certainty of the evidence, and other considerations
- Convening a public review of the guideline draft in February 2022
- Amending the guideline based on the external review feedback and updating the literature search
- Finalizing and publishing the guideline

Commissioning of Work Group and ERT for the guideline update

For the guideline update the previously assembled Work Group with expertise in adult nephrology, cardiology, endocrinology, dietetics, epidemiology, primary care, and public health, as well as people living with diabetes and kidney disease were engaged. Cochrane Kidney and Transplant, with expertise in adult and pediatric nephrology, evidence synthesis and guideline development, were again contracted as the ERT and tasked with updating the systematic evidence review. The ERT coordinated the methodological and analytical processes of guideline development, including literature searching, data extraction, critical appraisal, evidence synthesis and meta-analysis, grading the certainty of the evidence per outcome, and grading the certainty of the evidence for the recommendations. The Work Group was responsible for writing the recommendations and the underlying rationale, as well as grading the strength of the recommendation.

Defining scope and topics for the update of the guidelines

Due to resourcing and the probability of practice-changing studies, clinical questions on effectiveness and safety of interventions included in the guideline update were limited to RCTs. Guideline topics and clinical questions focusing on nonrandomized studies were not included in the guideline update

(Supplementary Table S1). For efficiency and prioritization of the guideline update, the Work Group identified key questions that were known to have newly published RCTs. Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accordingly. For clinical questions that did not map with Cochrane Kidney and Transplant systematic reviews, de novo systematic reviews were undertaken. Details of the Population, Intervention, Comparator, Outcome (list of critical and important outcomes detailed in Table 1), and Methods (PICOM) questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 2.[5-15] All evidence reviews were conducted in accordance with the Cochrane Handbook,[16] and guideline development adhered to the standards of GRADE (Grading of Recommendation, Assessment, Development, and Evaluation).[17]

Table 1. Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality • Cardiovascular mortality • Kidney failure • 3-point and 4-point major cardiovascular events (MACE) • Individual cardiovascular events (myocardial infarction, stroke, heart failure) • Doubling serum creatinine • Hypoglycemia requiring third-party assistance • Attaining HbA1c • HbA1c • Hyperkalemia
Important outcomes	• Albuminuria progression (onset of albuminuria, moderately increased to severely increased)
Non-important outcomes	• eGFR/creatinine clearance

eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MACE, major cardiovascular events.

Table 2. Clinical questions and systematic review topics in the PICOM format

Guideline chapter 1	Comprehensive care in patients with diabetes and CKD
Clinical question	Do RAS inhibitors improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	ACEi and ARB
Comparator	Standard of care/placebo
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: AKI, hyperkalemia
Study design	RCT
Cochrane systematic reviews	Strippoli *et al*. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev*. 2006; 6: CD006257.
SoF tables	Supplementary Tables S4, S5, S29, and S30
Clinical question	Does dual RAS inhibition compared to mono RAS inhibition improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	Dual RAS inhibition (ACEi and ARB)
Comparator	Mono RAS inhibition (ACEi or ARB)
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: AKI, hyperkalemia
Study design	RCT
Cochrane systematic reviews	Strippoli *et al*. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. *Cochrane Database Syst Rev*. 2006; 6: CD006257.
SoF tables	Supplementary Table S31
Clinical question	In patients with CKD and T2D, what are the effects of SGLT2i on clinically relevant outcomes and clinically relevant harms?
Population	Adults with CKD (G1-G5, G5D, G1T-G5T) and diabetes (T1D and T2D)
Intervention	SGLT2i
Comparator	Standard of care/placebo
Outcomes	Critical and important outcomes listed in Table 1 Long-term harms: hypoglycemia, lactic acidosis, amputation, bone fractures
Study design	RCT
Cochrane systematic reviews	Lo *et al*. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane Database Syst Rev*. 2018;9:CD011798 Lo *et al*. Glucose lowering agents for pre-existing and new onset diabetes in kidney transplant recipients. *Cochrane Database Syst Rev*. 2017;2:CD009966
SoF tables	Supplementary Tables S6, S32, S33, S79

Clinical question	Does the addition of medication blocking the action of aldosterone on RAS compared to standard of care or RAS inhibition alone improve clinically important outcomes and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	Mineralocorticoid receptor antagonist or direct renin inhibitors
Comparator	Standard of care or RAS inhibition
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: AKI, hyperkalemia
Study design	RCT
Cochrane systematic reviews	Andad *et al*. Direct renin inhibitors for preventing the progression of diabetic kidney disease (Protocol). *Cochrane Database Syst Rev*. 2013;9:CD010724 Bolignano *et al*. Aldosterone antagonists for preventing the progression of chronic kidney disease. *Cochrane Database Syst Rev*. 2014; CD007004
SoF tables	Supplementary Tables S7-S9, S34-S39
Clinical question	In patients with CKD with chronic hyperkalemia and diabetes mellitus, compared to usual care, does the use of potassium binders improve clinically relevant outcomes and reduce clinically relevant harms?
Population	Adults with CKD (G1-G5, G5D, G1T-G5T) and chronic hyperkalemia and diabetes (T1D and T2D)
Intervention	Potassium binders
Comparator	Standard of care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: AKI, hyperkalemia
Study design	RCT
Cochrane systematic reviews	Natale *et al*. Potassium binders for chronic hyperkalaemia in people with chronic kidney disease. *Cochrane Database Syst Rev*. 2020;6:CD013165
SoF tables	Supplementary Tables S42-S46
Clinical question	Do antiplatelet therapies improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D, G1T-G5T) and diabetes (T1D and T2D)
Intervention	Antiplatelet therapy
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: fatigue, blood pressure, quality of life
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S47-S49

Clinical question	Does smoking cessation versus usual care improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D, G1T-G5T) and diabetes (T1D and T2D)
Intervention	Smoking-cessation interventions
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S10
Clinical question	Does bariatric surgery versus usual care improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D, G1T-G5T) and diabetes (T1D and T2D)
Intervention	Bariatric surgery
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S57
Clinical question	In patients with diabetes and early CKD, do pharmaceutical weight-loss therapies, compared to placebo, no treatment, or standard care improve weight-loss or body-weight outcomes.
Population	Adults with CKD (G1-G5, G5D, G1T-G5T) and diabetes (T1D and T2D)
Intervention	Weight loss therapies (olistat, phentermine, saxenda, liraglutide, lorcaserin, bupropion-naltrexone, topiramate, acarbose, miglitol, pramlintide, exenatide, zonisamide, fluoxetide, semaglutide, dulaglutide)
Comparator	Placebo/standard of care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S83-S87
Guideline chapter 2	Glycemic monitoring and targets in patients with diabetes and CKD

Clinical question	In adults with diabetes and CKD, compared to HbA1c, do alternative biomarkers improve clinically relevant outcomes and decrease clinically relevant harms?
Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	Alternative biomarkers (glycated albumin, fructosamine, carbamylated albumin)
Comparator	HbA1c or blood glucose monitoring
Outcomes	All-cause mortality, end-stage kidney disease, CKD progression – doubling serum creatinine, ≥40% decline in eGFR, mean blood glucose (HbA1c)
Study design	RCT and observational studies
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Table S14
Clinical question	In adults with diabetes and CKD, compared to HbA1c, does blood glucose monitoring (CGM, SMBG) improve clinically relevant outcomes and decrease harms?
Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	Glucose monitoring (CGM, SMBG)
Comparator	HbA1c
Outcomes	All-cause mortality, kidney failure, CKD progression – doubling serum creatinine, ≥40% decline in eGFR, mean blood glucose (HbA1c)
Study design	RCT and observational studies
Cochrane systematic review	None relevant
SoF tables	Supplementary Table S15 and S50
Clinical question	Does reducing blood glucose to a lower versus higher target improve clinically relevant outcomes and intermediate outcomes, and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	Tight glycemic control (<7% HbA1c target or fasting glucose levels <120 mg/dl (6.7 mmol/l), <6.5% HbA1c target, or <6.0% HbA1c target)
Reference standard	Standard glycemic target
Outcomes	Outcomes listed in Table 1
Study design	RCT
Cochrane systematic reviews	Ruospo *et al*. Glucose targets for preventing diabetic kidney disease and its progression. *Cochrane Database Syst Rev*. 2017; CD010137
SoF tables	Supplementary Tables S11-S13
Guideline chapter 3	Lifestyle interventions in patients with CKD and diabetes
Clinical question	Does exercise/physical activity versus usual care improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?

Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	Exercise/physical activity (aerobic training, resistance training)
Comparator	Usual care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	Heiwe and Jacobson. Exercise training for adults with chronic kidney disease. *Cochrane Database of Sys Rev*. 2011; CD003236
SoF tables	Supplementary Tables S21 and S22
Clinical question	Do dietary interventions activity versus usual diet improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	Low-salt diets, low-potassium diets, low-phosphate diets, low-protein diets, dietary patterns (caloric restriction diet, whole food diets, Mediterranean diet, DASH diet, vegetarian diet)
Comparator	Usual diets
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: blood pressure, body mass index, body weight, fatigue, quality of life
Study design	RCT
Cochrane systematic reviews	McMahon *et al*. Altered dietary salt intake for people with chronic kidney disease. *Cochrane Database Syst Rev*. 2015;2:CD010070 Palmer *et al*. Dietary interventions for adults with chronic kidney disease. *Cochrane Database Syst Rev*. 2017;4:CD011998.
SoF tables	Supplementary Tables S16-S20 and S52-S56
Guideline chapter 4	Antihyperglycemic therapies in patients with diabetes and CKD
Clinical question	In patients with CKD and T2D, what are the effects of glucose-lowering medication on clinically relevant outcomes and clinically relevant harms?
Population	Adults with CKD (G1-G5, G5D, G1T-G5T) and diabetes (T1D and T2D)
Intervention	Older therapies - Metformin, insulin, sulfonylureas, or thiazolidinediones More recent therapies - alpha-glucosidase inhibitors, GLP-1 RA, DPP-4 inhibitors
Comparator	Standard of care/placebo
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes for GLP-1 RA: body weight, BMI Long-term harms: hypoglycemia, lactic acidosis, amputation, bone fractures
Study design	RCT
Cochrane systematic reviews	Lo *et al*. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. *Cochrane Database Syst Rev*. 2018;9:CD011798

	Lo *et al*. Glucose lowering agents for pre-existing and new onset diabetes in kidney transplant recipients. *Cochrane Database Syst Rev*. 2017;2:CD009966
SoF tables	Supplementary Tables S23, and S58-S91
Guideline chapter 5	Approaches to management of patients with diabetes and CKD
Clinical question	What are the most effective education, self-management education programs to improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	Education and self-management programs
Comparator	Standard of care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: fatigue and quality of life
Study design	RCT
Cochrane systematic reviews	Li *et al*. Education programmes for people with diabetic kidney disease. *Cochrane Database Syst Rev*. 2011;6:CD007374
SoF tables	Supplementary Tables S24-S25 and S92-S93
Clinical question	What are the most effective health care delivery programs to improve clinically relevant outcomes and reduce clinically relevant harms in patients with diabetes and CKD?
Population	Adults with CKD (G1-G5, G5D) and diabetes (T1D and T2D)
Intervention	Health service delivery programs/models of care
Comparator	Standard of care
Outcomes	Critical and important outcomes listed in Table 1 Additional outcomes: quality of life and fatigue
Study design	RCT
Cochrane systematic reviews	None relevant
SoF tables	Supplementary Tables S26-S28 and S94

ACEi, angiotensin-converting enzyme inhibitor(s); AKI, acute kidney injury; ARB, angiotensin II receptor blocker; BMI, body mass index; CGM, continuous glucose monitoring; CKD, chronic kidney disease; DASH, Dietary Approaches to Stop Hypertension; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; G, glomerular filtration rate category (suffix D denotes dialysis and suffix T denotes transplant recipient); G1T, CKD G1 after transplantation; G5D, CKD G5 treated by dialysis; G5T, CKD G5 after transplantation; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; PICOM, population, intervention, comparator, outcome, methods; RAS, renin–angiotensin system; RCT, randomized controlled trial; SCr, serum creatinine; SGLT2i, sodium–glucose cotransporter-2 inhibitor; SMBG, self-monitoring of blood glucose; SoF, Summary of findings; T1D, type 1 diabetes; T2D, type 2 diabetes.

Literature searches and article selection

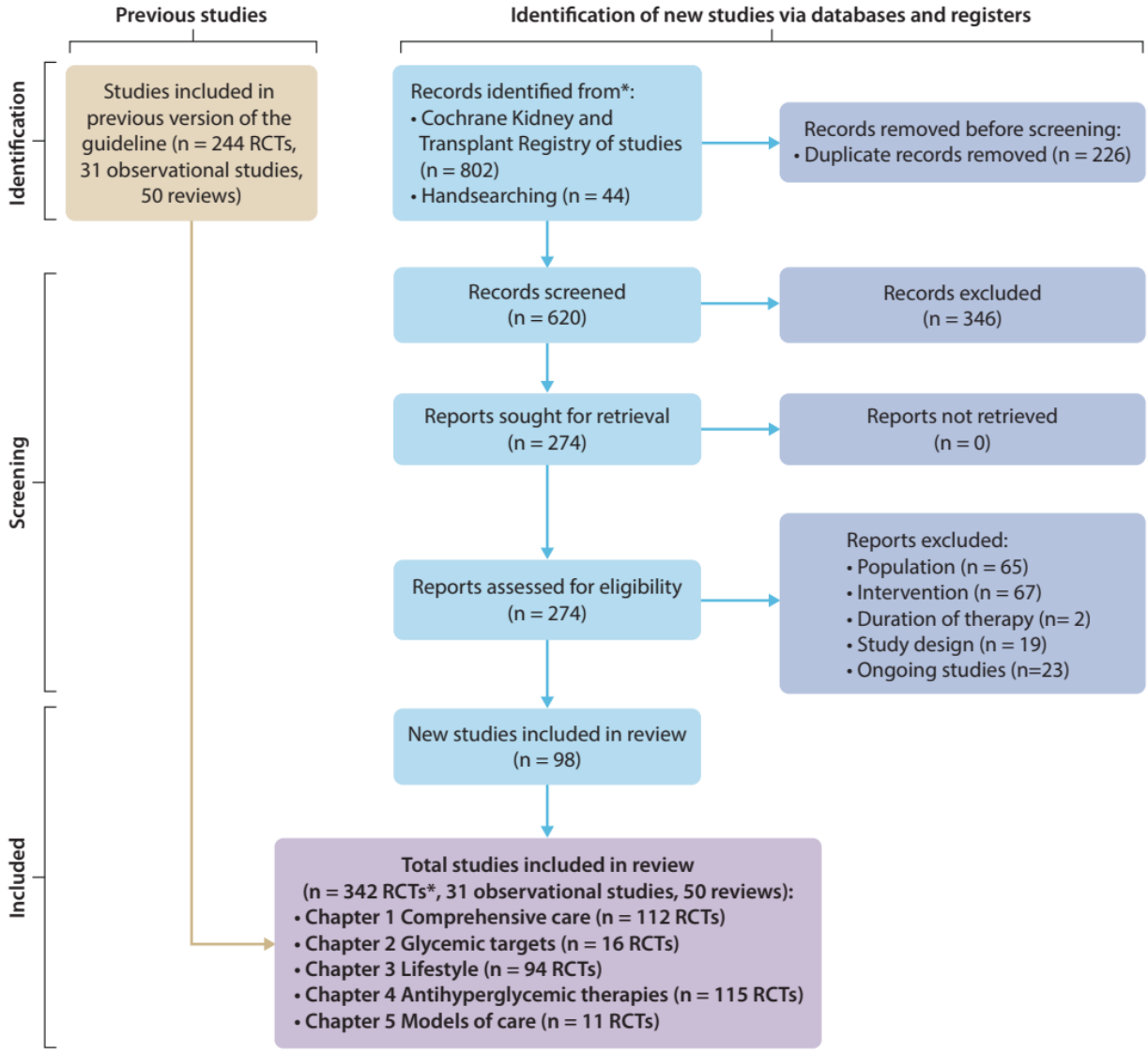
Searches for RCTs utilized the Cochrane Kidney and Transplant Registry of studies. The Cochrane Kidney and Transplant Registry of studies is a database of RCTs in kidney disease that is maintained by information specialists. The database is populated by monthly searches of the Cochrane Central Register of Controlled Trials, weekly searches of MEDLINE OVID, yearly searches of Embase OVID, hand-searching of major kidney and transplant conference proceedings, searches of trial registries, including clinicaltrials.gov, and the International Clinical Trials Register search portal.

For review topics that matched existing Cochrane Kidney and Transplant systematic reviews, an updated search of the Cochrane Kidney and Transplant Registry of studies was conducted. The Cochrane Kidney and Transplant Registry of studies was also searched for RCTs not associated with existing Cochrane systematic review. The search strategies are provided in Appendix A: Supplementary Table S1.

The titles and abstracts resulting from the searches were screened by a member of the ERT and confirmed independently by another member of the ERT, if necessary, the full text was assessed to determine its inclusion criteria. Disagreement about inclusion was resolved by discussion with a third member of the ERT.

The 2020 guideline search identified 5667 citations. The updated 2022 search identified 846 citations that were screened. Of these, 98 RCTs were included in the updated evidence review. In total 342 RCTs, 31 observational studies, and 50 systematic reviews have been included in the guideline (Figure 36).

Figure 36. Search yield and study flow diagram


Previous studies
Identification of new studies via databases and registers
Identification
Screening
Included
Studies included in previous version of the guideline (n = 244 RCTs, 31 observational studies, 50 reviews)
Records identified from*:
• Cochrane Kidney and Transplant Registry of studies (n = 802)
• Handsearching (n = 44)
Records removed before screening:
• Duplicate records removed (n = 226)
Records screened (n = 620)
Records excluded (n = 346)
Reports sought for retrieval (n = 274)
Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 274)
Reports excluded:
• Population (n = 65)
• Intervention (n = 67)
• Duration of therapy (n= 2)
• Study design (n = 19)
• Ongoing studies (n=23)
New studies included in review (n = 98)
Total studies included in review (n = 342 RCTs*, 31 observational studies, 50 reviews):
• Chapter 1 Comprehensive care (n = 112 RCTs)
• Chapter 2 Glycemic targets (n = 16 RCTs)
• Chapter 3 Lifestyle (n = 94 RCTs)
• Chapter 4 Antihyperglycemic therapies (n = 115 RCTs)
• Chapter 5 Models of care (n = 11 RCTs)

*A number of RCTs overlap across chapters in the guidelines RCT, randomized controlled trial.

Data extraction

Data extraction was performed independently by a member of the ERT, confirmed by the second member of the ERT. Unclear data were clarified by contacting the author of the study report, and any relevant data obtained in this manner were included. Any differences regarding how to perform extraction, among members of the ERT, were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Critical appraisal of studies

As the guideline update evidence review only included RCTs, The Cochrane Risk of Bias tool[18] was used to assess individual study limitations based on the following items:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?

- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
    - Participants and personnel (performance bias)
    - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias? Including an assessment of the study sponsor involvement in study design, conduct, and reporting[19]

All critical appraisal was conducted independently by 2 members of the ERT, with disagreements regarding the risk of bias adjudications resolved by consultation with a third review author.

Evidence synthesis and meta-analysis

The evidence synthesis and meta-analysis methods undertaken for the KDIGO 2020 diabetes and CKD guidelines were followed for the 2021 guideline update

Measures of treatment effect

Dichotomous outcome (all-cause mortality, cardiovascular mortality, kidney failure, cardiovascular events [MACE and individual events—myocardial infarction, stroke, heart failure], doubling of serum creatinine, moderately increased albuminuria to severely increased albuminuria progression, hypoglycemia requiring third-party assistance, etc.) results were expressed as RR with 95% CI. For time-to-event data (MACE), HRs with 95% CI were reported; when continuous scales of measurement were used to assess the effects of treatment, such as HbA1c etc., the mean difference (MD) with 95% CI was used.

Data synthesis

Data were pooled using the Mantel–Haenszel random-effects model for dichotomous outcomes and the inverse variance random-effects model for continuous outcomes. The random-effects model was chosen because it provides a conservative estimate of effect in the presence of known and unknown heterogeneity.[16] The generic inverse variance random-effects analysis was used for time-to-event data.

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes and of risk ratios, and χ^2 tests. A P <0.05 was used to denote statistical heterogeneity, with an I^2 calculated to measure the proportion of total variation in the estimates of treatment effect that was due to heterogeneity beyond chance.[16] We used conventions of interpretation as defined by Higgins *et al.*, 2003.[20]

Assessment of publication bias

We made every attempt to minimize publication bias by including unpublished studies (e.g., by searching online trial registries and conference abstracts). To assess publication bias, we used funnel plots of the log odds ratio (effect versus standard error of the effect size) when a sufficient number of studies were available (i.e., more than 10 studies).[16] Other reasons for the asymmetry of funnel plots were considered.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was undertaken to explore whether clinical differences between the studies may have systematically influenced the differences that were observed in the critical and important outcomes.

However, subgroup analyses are hypothesis-forming, rather than hypothesis-testing, and should be interpreted with caution. The following subgroups were considered: type of diabetes, severity of CKD, dialysis modality, age group (pediatric or older adults), and type of intervention—for example, short-acting versus long-acting GLP-1 RA. The test of subgroup differences used the I^2 statistic and a *P*-value of 0.1 (noting that this is a weak test).[16]

For Chapter 4. Antihyperglycemic therapies, subgroup analysis was undertaken to assess effect. modification of the population of the included studies. Studies that were designed specifically to assess the effects of antihyperglycemic therapy in people with CKD and T2D (e.g., CREDENCE) were compared to studies in people with T2D that reported subgroups of people with CKD (e.g., DECLARE TIMI 58) to assess any subgroup differences.

Sensitivity analyses

The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of the risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry versus other), and country in which the study was conducted

Grading the quality of the evidence and the strength of a guideline recommendation

Grading the quality of the evidence for each outcome across studies

The overall quality of the evidence related to each critical and important outcome was assessed using the GRADE approach,[17, 21] which assesses the quality of the evidence for each outcome. For outcomes that are based on data from RCTs, the initial grade for the quality of the evidence is considered to be high. The quality of the evidence is lowered in the event of study limitations; important inconsistencies in results across studies; indirectness of the results, including uncertainty about the population, intervention, outcomes measured in trials, and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, data were benchmarked against optimal information size,[21] low event rates in either arm, CIs that indicate appreciable benefit and harm (25% decrease and 25% increase in the outcome of interest), and sparse data (only 1 study), all indicating concerns about the precision of the results.[21] The final grade for the certainty of the evidence for an outcome could be high, moderate, low, or very low (Table 3 & Table 4).

Table 3. Classification for certainty and quality of the evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.

D	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.

Table 4. GRADE system for grading the quality of evidence

Study design	Staring grade of the quality of the evidence	Step 2 – lower the grade	Step 3 – raise the grade for observational studies
RCT	High	Study limitations: -1, serious	Strength of association +1, large effect size (e.g.,
	Moderate	-2, very serious Inconsistency:	<0.5 or >2) +2, very large effect size
Observational	Low	-1, serious -2, very serious	(e.g., <0.2 or >5)
	Very low	Indirectness: -1, serious -2, very serious	Evidence of a dose response gradient
		Imprecision: -1, serious -2, very serious	All plausible confounding would reduce the demonstrated effect
		Publication bias: -1, serious -2, very serious	

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; RCT, randomized controlled trial

Summary of findings (SoF) tables

The SoF tables were developed to include a description of the population and the intervention and comparator. In addition, the SoF tables included results from the data synthesis as relative and absolute effect estimates. The grading of the quality of the evidence for each critical and important outcome is also provided in these tables. The SoF tables are available in the Data Supplement published alongside the guideline or at https://kdigo.org/guidelines/diabetes-ckd/org.

Updating and developing the recommendations

The guideline statements from the KDIGO 2020 Management of Diabetes in CKD Guideline[1] were considered in the context of new evidence by the Work Group Co-Chairs and Work Group members, and updated as appropriate. Recommendations were revised during virtual meetings in 2021 and by e-mail communication. The final draft was sent for external public review, and reviewers provided feedback for consideration by the Work Group. Based on feedback, the guideline was further revised by Work Group, as appropriate. All Work Group members provided input on initial and final drafts of the recommendation statements and guideline text and approved the final version of the guideline. The ERT also provided a descriptive summary of the *Quality of evidence* in support of the graded recommendations.

Grading the strength of the recommendations

The strength of a recommendation is graded as strong or weak (Table 5). The strength of a recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall certainty of the evidence, patient values and preferences, resource use and costs, and other considerations (Table 6).

Table 5. KDIGO nomenclature and description for grading recommendations

Grade	Implications		
	Patients	**Clinicians**	**Policy**
Level 1, "Strong" "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2, "Weak" "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

KDIGO, Kidney Disease: Improving Global Outcomes.

Table 6. Determinants of the strength of recommendation

Factors	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a strong recommendation is provided. The narrower the gradient, the more likely a weak recommendation is provided.
Quality of the evidence	The higher the quality of the evidence, the more likely a strong recommendation is warranted. However, there are exceptions for which low or very low quality of the evidence will warrant a strong recommendation.
Values and preferences	The more variability or the more uncertainty in values and preferences, the more likely a weak recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed in the judgment of the Work Group when robust evidence was not identified.
Resources and other considerations	The higher the cost of an intervention—that is, the more resources consumed—the less likely a strong recommendation is warranted.

Balance of benefits and harms

The Work Group and ERT determined the anticipated net health benefit on the basis of expected benefits and harms across all critical and important outcomes from the underlying evidence review.

The overall quality of the evidence

The overall quality of the evidence was based on the quality of evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall quality of the evidence was graded A, B, C, or D (Table 3).

Patient preferences and values

The Work Group included 2 people living with diabetes and CKD. These members' unique perspectives and lived experience, in addition to the Work Group's understanding of patient preferences and priorities, also informed decisions about the strength of the recommendation. A systematic review on qualitative studies on patient priorities and preferences was not undertaken for the guideline.

Resources and other considerations

Health care and non–health care resources, including all inputs in the treatment management pathway, were considered in grading the strength of a recommendation.[22] The following resources were considered: direct health care costs, non–health care resources (such as transportation and social services), informal caregiver resources (e.g., time of family and caregivers), and changes in productivity. No formal economic evaluations, including cost-effectiveness analysis, were conducted.

Practice points

In addition to graded recommendations, KDIGO guidelines include "practice points" to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care and supplement recommendations for which a larger quality of evidence was identified. These were developed when no formal systematic evidence review was undertaken or if there was insufficient evidence to provide a graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they may be based on limited evidence. Practice points are sometimes formatted as a table, a figure, or an algorithm, to make them easier to use in clinical practice.

Format for guideline recommendations

Each guideline recommendation provides an assessment of the strength of the recommendation (strong, level 1 or weak, level 2) and the quality of the evidence (A, B, C, D). The recommendation statements are followed by key information (benefits and harms, quality of the evidence, values and preferences, resource use and costs, considerations for implementation), and rationale. Each recommendation is linked to relevant SoF tables. In most cases, an underlying rationale supported each practice point.

Limitations of the guideline development process

The evidence review for the guideline prioritized RCTs as the primary source of evidence, and study types beyond RCTs have not been considered for the guideline update. However, considering the short-time frame between the previous guideline version (2020)[1] and the guideline update (2022), there is unlikely to be practice changing evidence beyond RCTs. The search strategy for the guideline update has relied on a well-maintained expertly controlled database of RCTs in kidney disease. However, the search strategies were not exhaustive, as specialty or regional databases were not searched, and hand-searching of journals was not performed for the included reviews. Two people living with diabetes and kidney

disease were members of the Work Group and provided an invaluable perspective and lived experience for the development of these guidelines. However, in the development of these guidelines, no scoping exercise with patients, searches of the qualitative literature, or formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, no economic evaluations were undertaken.

References:

1. Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2020; **98:** S1-S115.

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